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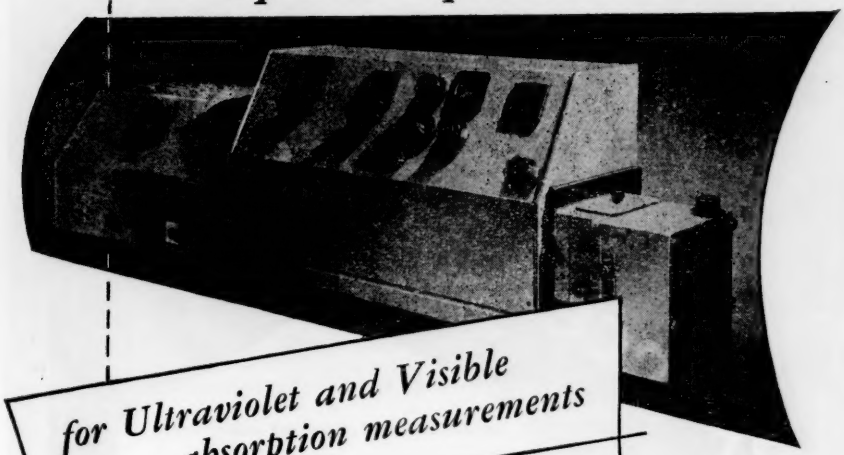

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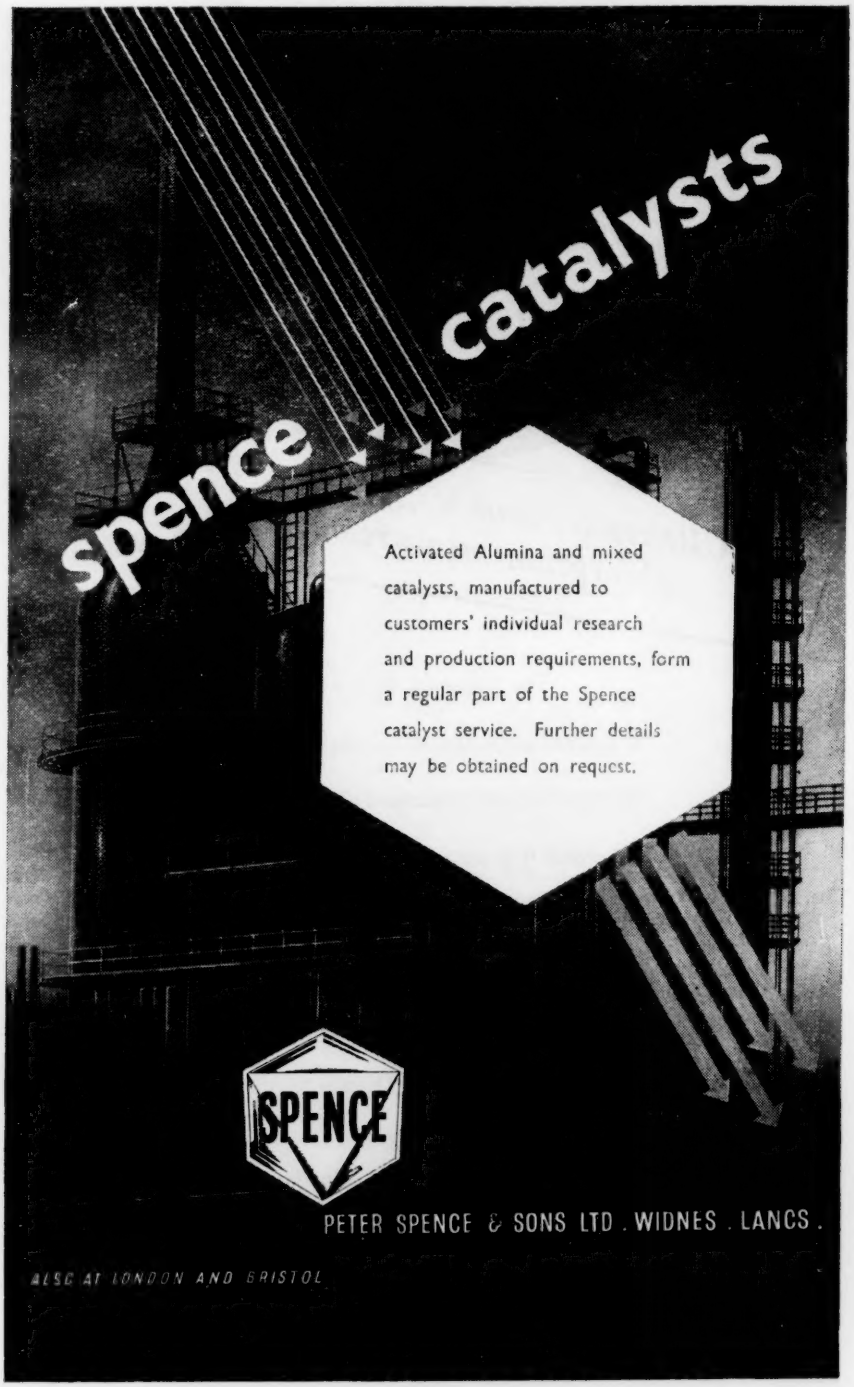
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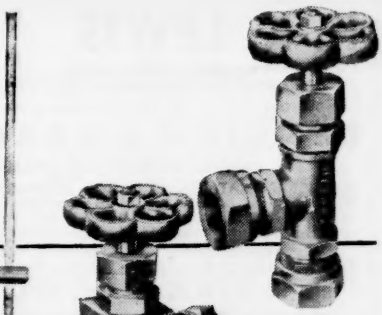

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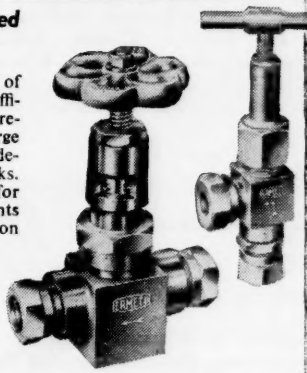

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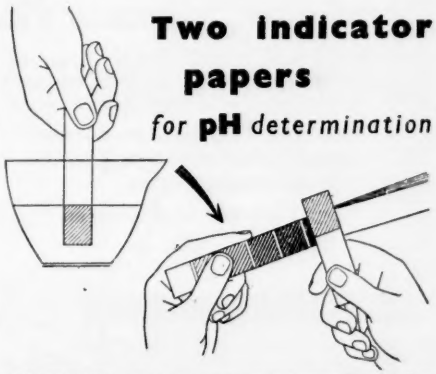

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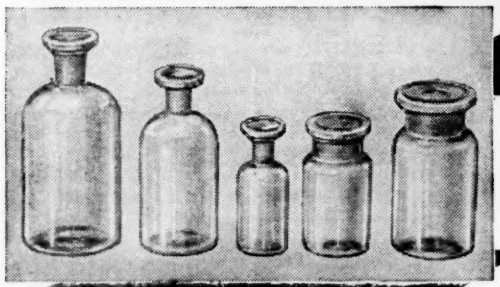

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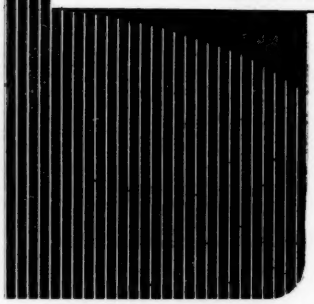

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Whiting, M. C. See Bates, E. B., 1854, Eglinton, G., 1860, and Jones, E. R. H., 1865.
Williams, L. T. D. See Neale, E., 2156.
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Xuong, Ng. D. See Nam, Ng. H., 1690, and Sy, M., 1975.
Youngson, G. W. See Watson, M. B., 2145.

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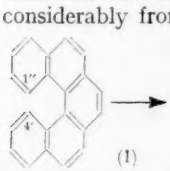
The Crystal Structure and Molecular Shape of 3 : 4-5 : 6-*Dibenzophenanthrene.*

By A. O. McIntosh, J. Monteath Robertson, and V. Vand.

[Reprint Order No. 4861.]

A detailed *X*-ray structural investigation has been made of 3 : 4-5 : 6-dibenzophenanthrene, the monoclinic crystalline modification which contains twelve molecules in the unit cell being used. Four of these molecules are found to display an exact two-fold axis of symmetry, while the other eight occupy general positions in the space group (C_{2h}^6) which do not demand any molecular symmetry. The molecules are found to be severely distorted from the planar configuration, the two naphthalene wings being bent away from each other so as to achieve a clearance of about 3·0 Å between the non-bonded carbon atoms 4′ and 1″. This bending is distributed over the five fused rings in such a manner as to cause no very severe buckling or angle distortion in any individual ring, and so the retention of aromatic properties can be understood. The two optical isomers are present in the unit cell, related to each other as required by the symmetry elements of the space group. Although approximate co-ordinates have been found for all the atoms, the accuracy is not high (about ±0·1 to ±0·2 Å) and no significant determinations of bond lengths within the molecule can be made.

The structure of 3 : 4-5 : 6-dibenzophenanthrene (I) is of interest because it must depart considerably from the usual regularity of aromatic hydrocarbons (see, *e.g.*, Cook, *Ann. Reports*, 1942, **39**, 155, 173). To allow sufficient clearance between the non-bonded carbon atoms 4′ and 1″, with their attached hydrogen atoms, there must be either a very severe distortion of the angles and bond lengths in the aromatic rings, or else the molecule must assume a non-planar form. That the second possibility is the one mainly operative appears to be established by the work of Bell and Waring (*J.*, 1949, 2689) who succeeded in isolating optically active forms of 2′ : 2″-4′ : 4″-tetramethyl-3 : 4-5 : 6-dibenzophenanthrene-9 : 10-dicarboxylic acid, and more recently by Hall and Turner (*Chem. and Ind.*, 1953, 1177) who have prepared optically active 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene.



(I)

We have now attempted to determine the exact nature of the molecular distortion in 3 : 4-5 : 6-dibenzophenanthrene by means of a detailed *X*-ray crystallographic investigation, and some preliminary results have been reported (McIntosh, Robertson, and Vand, *Nature*, 1952, **169**, 322). Unfortunately, the monoclinic modification of the compound which we have investigated is extremely complex, containing twelve molecules in the unit cell. In spite of repeated refinements by the double Fourier series method, in which the XRAC computer (Pepinsky, *J. Appl. Physics*, 1947, **18**, 601) has been employed, and by a large number of difference syntheses, the final accuracy is not high, although it is sufficient to establish the general features of the structure. It had been hoped to pursue this analysis further by means of the three-dimensional Fourier series method, but in the meantime a much simpler crystalline modification has been discovered by Harnick, Herbstein, and Schmidt (*Nature*, 1951, **168**, 158) which contains only four molecules in the monoclinic cell. It would therefore be more reasonable to conduct any further refinement of the molecular structure on this second and simpler modification.

Crystal Data.—3 : 4-5 : 6-Dibenzophenanthrene, $C_{22}H_{14}$; *M*, 278·3; m. p. 177—178°; *d*, calc. 1·253, found 1·264. Monoclinic, $a = 26{\cdot}17 \pm 0{\cdot}15$, $b = 8{\cdot}94 \pm 0{\cdot}03$, $c = 19{\cdot}57 \pm 0{\cdot}07$ Å, $\beta = 105{\cdot}1° \pm 0{\cdot}3°$. Absent spectra, (*h*0*l*) when *h* is odd and when *l* is odd, (0*k*0) when *k* is odd, (*hkl*) when $k + l$ is odd. Space group, C_s^4–*Aa* or C_{2h}^6–*A*2/*a*. The results of this analysis indicate C_{2h}^6. Twelve molecules per unit cell. Molecular symmetry, two-fold axis in four of the molecules. Volume of the unit cell = 4419 Å^3. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$) $\mu = 6{\cdot}6$ per cm. Total number of electrons per unit cell = F(000) = 1752.

The absent spectra do not permit an unambiguous determination of space group, and the possibilities, C_s^4 or C_{2h}^6, must be distinguished by other means. The unusually large number of molecules in the unit cell suggests the group of higher symmetry. More direct confirmation was obtained by making a statistical survey of the intensities of the (*h*0*l*) and (*hk*0) zones, using the procedure of Howells, Phillips, and Rogers (*Acta Cryst.*, 1950, **3**, 210). The distributions obtained were decisively in favour of a centrosymmetrical structure, as shown by Fig. 1, and thus pointed clearly to the space group C_{2h}^6.

The crystals of the present twelve-molecule modification of dibenzophenanthrene were obtained from ethyl alcohol solution and occur as well-developed bipyramids, the faces identified being (100), (101), (010), and (11$\bar{1}$). When the compound is recrystallized from acetic acid, Harnick, Herbstein, and Schmidt's four-molecule monoclinic modification (*loc. cit.*) is obtained in the form of needles.

Analysis of the Structure.—A very unusual feature of this crystal structure, and one which greatly increases the complexity of the analysis, is the presence of twelve chemical

FIG. 1. *Distribution of* (*h*0*l*) *and* (*hk*0) *intensities; z is a fraction of the local averaged intensity; N*(*z*) *is the fraction of the reflections with intensities equal to or less than z; full curve is the theoretical distribution for a centrosymmetrical structure, broken curve for non-centrosymmetrical.*

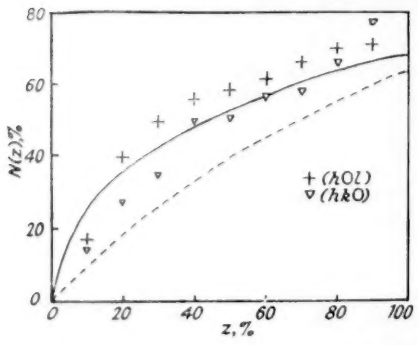
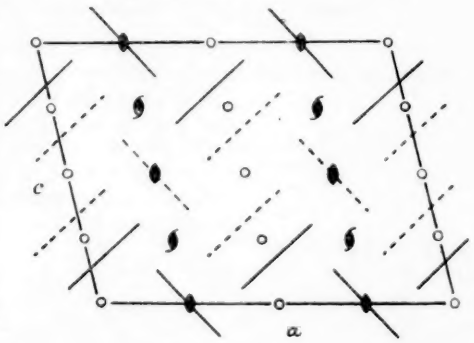


FIG. 2. *Relative positions of the molecules in the unit cell, viewed along the two-fold axis. Broken lines represent molecules displaced* ½b *with respect to the others. Small circles denote symmetry centres, ovals diad axes.*



molecules in the unit cell. If the space group is assumed to be C_{2h}^6 in accordance with the facts mentioned above, then the unit cell must contain eight equivalent asymmetric units. It follows that the asymmetric unit must consist of 1½ chemical molecules. Now, a molecule can only be shared between two equivalent asymmetric units if it contains an inherent element of symmetry required by the space group, that is, if it happens to coincide with one of the space-group symmetry elements. From the chemical formula (I) it is clear that the molecule cannot have a centre of symmetry, and thus the only possible symmetry is a two-fold axis, which must be parallel to the *b* crystallographic axis. This analysis therefore requires the four shared molecules to lie on the two-fold axes in the special positions $\frac{1}{4}, y, 0$; $\frac{3}{4}, \bar{y}, 0$; $\frac{1}{4}, y+\frac{1}{2}, \frac{1}{2}$; $\frac{3}{4}, \frac{1}{2}-y, \frac{1}{2}$. The remaining eight molecules can then lie in the eight general positions of the space group. Taking an origin at a centre of symmetry, the co-ordinates of these positions are $\pm(x, y, z;\ \frac{1}{2}-x, y, \bar{z};\ x, y+\frac{1}{2}, z+\frac{1}{2};\ \frac{1}{2}-x, y+\frac{1}{2}, \frac{1}{2}-z)$. Such a distribution of the molecules between both general and special positions is unusual, but a somewhat similar situation has been reported for diphenylene (Waser and Lu, *J. Amer. Chem. Soc.*, 1944, **66**, 2035) and for bisdiphenyleneethylene (Fenimore, *Acta Cryst.*, 1948, **1**, 295).

The distribution of the molecules as postulated above imposes certain limits on their possible arrangement and orientation. In particular, the two-fold symmetry axes (see I) of the molecules in special positions must be parallel to *b*, producing an end view of these molecules when viewed in projection on the (010) plane. The length of the *b* crystal axis (8·94 Å) is sufficient to accommodate a molecule in this position, and the great strength

of the (080) reflection (F = 97) is explained because its period then corresponds approximately to the spacing between the rows of carbon atoms lying normal to the *b* axis.

When four molecules are placed in these special positions it is found that the sites of the remaining eight molecules are restricted by packing considerations. Although not required to display any exact two-fold axis, these molecules must be set up in a somewhat similar way so that they also appear in end view on the (010) projection. Further, it is observed that the (*h*0*l*) reflections are on the average much stronger than those of the other two axial zones; and amongst the (*h*0*l*) reflections the (402), (40$\bar{4}$), (60$\bar{4}$), (60$\bar{6}$), (8,0,$\bar{1}$0), (10,0,4), (10,0,$\bar{1}$0), and (14,0,4) are very strong. These facts are consistent with the diagonal packing of the molecules illustrated in Fig. 2.

Refinement of the Structure.—Chemical considerations already mentioned show that the molecule of 3 : 4-5 : 6-dibenzophenanthrene cannot be planar, and so the end view along the two-fold axis cannot truly be represented by the simple lines in Fig. 2. Some direct *X*-ray evidence concerning the molecular distortion can be obtained from the (015) reflection, which is very strong. The form of the structure factor function for this reflection shows that it is not possible for any planar configuration of the carbon atoms to account for such a high value. The distortion required can be obtained by bending the two

FIG. 3. *Electron-density projection on* (010) *covering two molecules of* 3 : 4-5 : 6-*dibenzophenanthrene, with final co-ordinates superimposed. Contour interval,* 2 *e.*Å^{-2}, *the two-electron line being dotted.*

naphthalene wings of the molecule in opposite directions out of the mean plane, which is represented by the short lines in Fig. 2. In this way, a reasonable trial model for the molecule was set up and adjusted until it yielded some measure of agreement between the observed and calculated structure factors.

An attempt was next made to refine the *x* and *z* co-ordinates of the atoms by the Fourier method, employing the (*h*0*l*) structure factors and the projection along the relatively short *b* axis (8·94 Å). In the first synthesis 41 measured structure factors were employed, and although only vague groups of atoms could be distinguished it was at once clear that a distortion in the wrong direction had been applied to the molecules in the special positions. The sense of this distortion was then reversed, and further Fourier syntheses were computed.

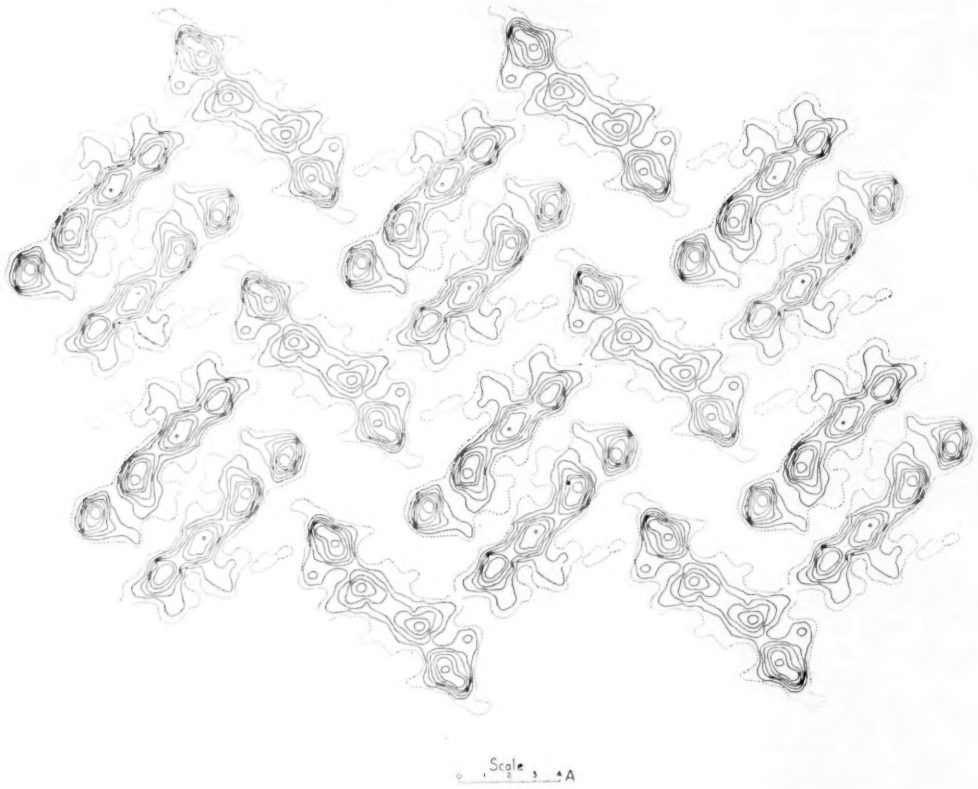
At this point it became possible through the courtesy of Professor Pepinsky to employ the *X*-Ray Analogue Computer (XRAC) at Pennsylvania State College on the refinement process (Pepinsky, *J. Appl. Physics*, 1947, **18**, 601). In this work background criteria were employed to indicate the probable signs of some of the smaller structure factors, but the refinement process was greatly hampered by the fact that few separately resolved atoms can be expected in any projection of the structure owing to the complex interleaving of the molecules. The final projection from the computer had well-developed detail in the outspread parts of the molecule which indicated the general form of the distortion but still left considerable latitude in choosing atomic co-ordinates.

Further refinement of the co-ordinates was achieved by means of difference syntheses.

After the computation of 13 of these the discrepancy between the observed and calculated structure factors of the 146 (*h*0*l*) planes employed had decreased to 27%. At this stage the structure appears to be reasonably certain, although not sufficiently precise to permit significant calculations of all the individual C–C bond lengths within the molecule. A final electron-density projection on (010) showing the two crystallographically independent molecules is shown in Fig. 3, and Fig. 4 shows on a smaller scale the mutual arrangement of all the molecules in the unit cell.

Co-ordinates.—The *x* and *z* co-ordinates were obtained from the above Fourier syntheses and from the difference syntheses, while the *y* co-ordinates were adjusted mainly by trial

FIG. 4. *Electron-density projection on* (010) *covering whole unit cell.* (*This map is based on an earlier and less refined Fourier synthesis than Fig.* 3.)



and error, the (*hk*0) and (0*kl*) reflections being used. The final values of the co-ordinates for the 33 carbon atoms in the asymmetric unit are given in Table 1. The origin is taken at a centre of symmetry. Atoms lettered *A* to *K* refer to one-half of the molecule lying on the diad axis (see Fig. 2 and Fig. 5), the co-ordinates of the atoms forming the other half of this molecule being given by ($\frac{1}{2}a - x, y, -z$). Atoms lettered *A′* to *K′* and *A″* to *K″* refer to the two corresponding halves of the other molecule lying in the general position. *x*, *y*, *z* are monoclinic co-ordinates expressed as fractions of the axial lengths; *X*, *Y*, *Z* are in Ångstrom units, and *X′* and *Z′* are orthogonal co-ordinates in Ångstrom units, referred to the *a* and *b* crystal axes and their perpendicular *c′*.

Discussion of Results.—The refinement of the structure has not proceeded far enough to enable the carbon–carbon bond lengths within the molecule to be determined with any

TABLE 1. *Co-ordinates.*

Atom	x	y	z	X	Y	Z	X'	Z'
A	0·247	0·636	0·031	6·46	5·68	0·61	6·30	0·59
B	0·233	0·498	0·061	6·10	4·45	1·20	5·79	1·16
C	0·220	0·498	0·126	5·76	4·45	2·46	5·12	2·38
D	0·201	0·358	0·158	5·26	3·20	3·09	4·46	2·98
E	0·198	0·222	0·114	5·18	1·98	2·23	4·60	2·15
F	0·176	0·089	0·144	4·61	0·80	2·82	3·88	2·72
G	0·158	0·965	0·094	4·13	8·62	1·83	3·65	1·77
H	0·163	0·975	0·022	4·27	8·71	0·42	4·16	0·41
I	0·196	0·095	0·006	5·12	0·85	0·12	5·09	0·12
J	0·210	0·225	0·044	5·49	2·01	0·86	5·27	0·83
K	0·234	0·358	0·022	6·12	3·20	0·43	6·01	0·42
A'	0·008	0·114	0·162	0·22	1·02	3·17	−0·61	3·06
B'	−0·014	0·253	0·132	−0·38	2·26	2·58	−1·05	2·49
C'	−0·066	0·253	0·095	−1·74	2·26	1·85	−2·22	1·79
D'	−0·088	0·392	0·067	−2·29	3·51	1·30	−2·63	1·26
E'	−0·056	0·525	0·069	−1·45	4·69	1·35	−1·80	1·30
F'	−0·071	0·645	0·022	−1·86	5·76	0·43	−1·97	0·42
G'	−0·033	0·765	0·014	−0·87	6·84	0·27	−0·94	0·26
H'	0·019	0·765	0·050	0·49	6·84	0·97	0·24	0·94
I'	0·038	0·637	0·093	1·00	5·69	1·83	0·52	1·77
J'	0·000	0·522	0·107	0·00	4·66	2·10	−0·55	2·03
K'	0·012	0·392	0·142	0·31	3·51	2·78	−0·41	2·68
A''	0·067	0·117	0·198	1·76	1·05	3·87	0·75	3·74
B''	0·092	0·253	0·234	2·40	2·26	4·58	1·21	4·42
C''	0·148	0·253	0·277	3·87	2·26	5·42	2·46	5·23
D''	0·175	0·392	0·307	4·58	3·51	6·00	3·02	5·79
E''	0·145	0·531	0·298	3·79	4·75	5·83	2·27	5·63
F''	0·166	0·665	0·339	4·34	5·94	6·63	2·61	6·40
G''	0·136	0·793	0·342	3·56	7·09	6·69	1·82	6·46
H''	0·085	0·790	0·301	2·21	7·06	5·89	0·68	5·69
I''	0·061	0·656	0·257	1·60	5·86	5·03	0·29	4·86
J''	0·091	0·533	0·249	2·38	4·77	4·87	1·11	4·70
K''	0·060	0·395	0·211	1·58	3·53	4·13	0·50	3·99

accuracy. The co-ordinates in Table 1 yield values for these bond lengths which vary from 1·3 to 1·6 Å. They are not reported individually because they are subject to errors of between ±0·1 and ±0·2 Å at the present stage of the analysis. The actual bond-length variation in a molecule of this type is likely to be from 1·35 to 1·50 Å, as in ovalene (Donaldson and Robertson, *Proc. Roy. Soc.*, 1953, *A*, **220**, 157) and perylene (Donaldson, Robertson, and White, *ibid.*, p. 311). In the present structure some of the longest bonds appear to be those connecting the two naphthalene wings of the molecule in the general position ($A'A''$ and $K'K''$); these are the bonds which are probably subject to the greatest twisting strain and distortion. This result cannot be confirmed for the other molecule, however, because the resolution is here too poor to enable any conclusions to be drawn.

Although no definite results can be obtained regarding individual bond-length variations, the nature of the molecular distortion can be ascertained with some certainty from this analysis. Its general form will be clear from a study of the projection of the molecules along the direction of the two-fold axis (Fig. 5).

In a coplanar, undistorted molecule the distance between the non-bonded carbon atoms I' and I'' would be about 1·4 Å. For the molecule in the general position we find this distance to be 3·1 Å, and for the molecule in the special position, 2·9 Å. These measurements are subject to a maximum error of about ±0·2 Å, and the mean value of 3·0 Å may be taken as indicating the magnitude of the displacement. This distortion is achieved without any very great change in the carbon valency angles or severe buckling of any individual benzene ring. Instead, the bending is distributed over the five fused rings in a manner similar to that which occurs when a rigid molecular model is forcibly distorted by bending the two wings apart. Such a distortion, which does not greatly disturb the trigonal symmetry of the bonds about any particular carbon atom, is compatible with the observed retention of aromatic character.

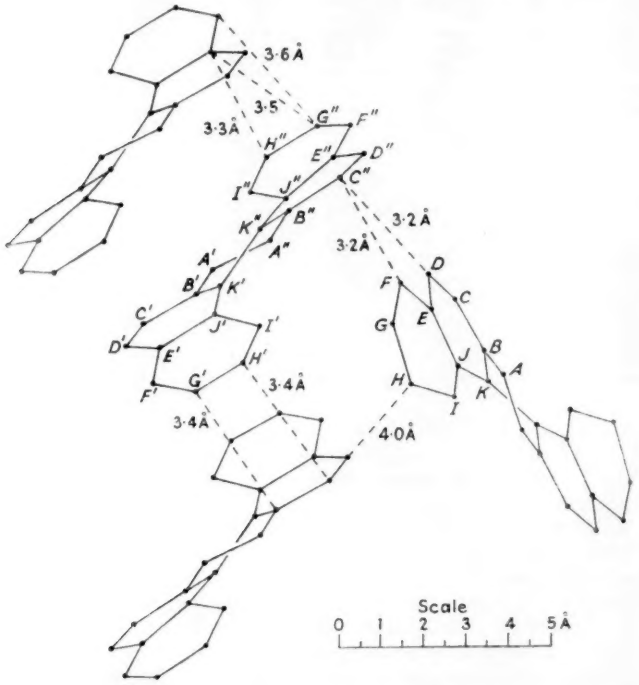
As required by the symmetry of the space group, the molecule in the special position lies with its two-fold axis perpendicular to the (010) plane, and in Fig. 5 this molecule (on

the right) shows an exact centre of symmetry in the projection. The other molecules in the general positions probably also have an exact two-fold symmetry axis, but in this case the axis appears to be tilted a few degrees away from the perpendicular position.

The compound, being a synthetic product, contains the expected two possible optical isomers in equal proportions. The two isomers present in the unit cell are related as demanded by the symmetry elements (Fig. 2)—the centres of symmetry, for example, requiring the axes of alternate molecules to be directed up and down respectively.

Intermolecular approach distances are indicated in Fig. 5. Again these are subject to possible errors of up to $\pm 0{\cdot}2$ Å, but within these limits they are found to conform to the minimum distances usual for aromatic hydrocarbon structures. For the pair of

FIG. 5. *Projection of part of the unit cell on* (010), *showing intermolecular contacts.*



molecules related by a centre of symmetry and lying in the general position the distance between carbon atom *G* of one and *B* of the other is 3·4 Å. Between *H* and *G* of the same pair of molecules the distance is also 3·4 Å. Between *F* and *D* of a molecule in the special position and *C* of the nearest one in the general position the distances are both 3·2 Å. Between *H* (special) and *D* (general) the distance is 4·0 Å. Between the other pair of molecules in the general position approaches of 3·5 Å (*G* . . . *E*), 3·6 Å (*G* . . . *F*), and 3·5 Å (*H* . . . *E*) are found.

EXPERIMENTAL

Copper radiation ($\lambda = 1{\cdot}542$ Å) and photographic methods were used throughout this study Visual estimates of intensities were made from moving-film records, the multiple film technique being used (Robertson, *J. Sci. Instr.*, 1943, **20**, 175). The crystal specimens employed were small bipyramids about 0·5 mm. by 0·4 mm. in cross section, although some slightly larger specimens were used to record the fainter reflections. The crystals were completely bathed in a uniform *X*-ray beam, and absorption corrections were not applied because of the approximately square cross section. The mosaic crystal formula was assumed, and the resulting

structure factors are given in Table 2 (F_0). The absent reflections and a few very weak ones are omitted from this table.

TABLE 2. *Measured and calculated structure factors.*

hkl	F_0	F_c	*hkl*	F_0	F_c	*hkl*	F_0	F_c	*hkl*	F_0	F_c
000	—	1752	16,0,6	38	30	10,0,$\bar{12}$	10	−2	20,2,0	24	12
200	66	91	14,0,6	43	−22	12,0,$\bar{12}$	40	−47	21,2,0	30	1
400	84	110	12,0,6	18	15	14,0,$\bar{12}$	34	−50	22,2,0	31	27
600	60	44	10,0,6	33	−17	18,0,$\bar{12}$	23	−26	340	29	−26
800	138	−112	806	34	50	20,0,14	16	10	440	51	−31
10,0,0	26	−16	606	69	99	14,0,14	9	−19	540	10	15
12,0,0	107	119	406	9	−3	12,0,14	25	−37	640	34	33
14,0,0	72	91	206	8	−33	6,0,14	25	31	740	10	61
30,0,0	16	12	20$\bar{6}$	174	−173	4,0,14	9	8	840	45	59
020	56	−56	40$\bar{6}$	117	87	2,0,14	16	6	940	37	27
040	39	41	60$\bar{6}$	203	171	2,0,$\bar{14}$	14	15	10,4,0	42	8
060	12	−29	80$\bar{6}$	51	−4	4,0,$\bar{14}$	12	−39	11,4,0	21	−19
080	97	99	10,0,$\bar{6}$	61	74	6,0,$\bar{14}$	8	−4	13,4,0	22	−9
002	27	27	12,0,$\bar{6}$	13	14	8,0,$\bar{14}$	8	−3	14,4,0	39	43
004	15	23	14,0,$\bar{6}$	23	−8	10,0,$\bar{14}$	15	−28	15,4,0	23	−26
006	16	30	16,0,$\bar{6}$	21	15	12,0,$\bar{14}$	58	38	16,4,0	65	−72
008	25	35	18,0,$\bar{6}$	43	27	14,0,$\bar{14}$	42	42	17,4,0	14	−32
0,0,10	16	−10	32,0,$\bar{6}$	20	−16	18,0,$\bar{14}$	38	−27	20,4,0	25	10
0,0,12	18	−5	18,0,8	31	−17	30,0,$\bar{14}$	24	−14	21,4,0	15	28
0,0,20	32	24	16,0,8	25	−18	10,0,16	29	40	22,4,0	26	10
0,0,22	23	−28	14,0,8	16	−23	8,0,16	22	−18	23,4,0	14	−16
16,0,2	18	2	10,0,8	21	32	4,0,$\bar{16}$	13	−11	25,4,0	13	3
14,0,2	41	−51	808	35	28	6,0,$\bar{16}$	42	−43	26,4,0	13	1
12,0,2	59	−75	608	55	6	12,0,$\bar{16}$	40	−36	30,4,0	13	−7
10,0,2	83	−87	408	91	102	14,0,$\bar{16}$	26	−20	260	38	−48
802	44	70	208	7	−10	20,0,$\bar{16}$	24	3	560	22	4
602	193	−167	20$\bar{8}$	6	16	28,0,$\bar{16}$	18	−25	660	13	−35
402	284	341	40$\bar{8}$	73	−34	10,0,18	16	17	960	14	27
202	137	−93	60$\bar{8}$	74	78	6,0,18	44	50	10,6,0	29	−43
20$\bar{2}$	121	−124	10,0,$\bar{8}$	67	85	4,0,18	30	32	11,6,0	14	−35
40$\bar{2}$	124	97	12,0,$\bar{8}$	15	−5	18,0,$\bar{18}$	24	−7	12,6,0	14	−3
60$\bar{2}$	155	161	16,0,$\bar{8}$	23	22	10,0,20	9	12	15,6,0	25	−1
80$\bar{2}$	7	−6	30,0,$\bar{8}$	21	22	8,0,20	10	−1	17,6,0	25	−2
10,0,$\bar{2}$	69	88	16,0,10	25	27	2,0,20	19	25	18,6,0	14	29
12,0,$\bar{2}$	15	3	14,0,10	21	2	4,0,$\bar{20}$	14	−16	180	15	18
14,0,$\bar{2}$	55	−45	10,0,10	22	−16	8,0,$\bar{20}$	13	−31	280	25	21
26,0,$\bar{2}$	23	37	8,0,10	8	−4	10,0,$\bar{20}$	18	12	380	31	−28
18,0,4	16	−15	6,0,10	11	−13	12,0,$\bar{20}$	18	1	480	44	42
16,0,4	28	1	4,0,10	8	2	16,0,$\bar{20}$	31	10	580	25	4
14,0,4	80	−84	2,0,10	19	−31	18,0,$\bar{20}$	19	19	980	15	−24
12,0,4	23	27	2,0,$\bar{10}$	58	68	120	6	−32	11,8,0	30	12
10,0,4	149	−133	4,0,$\bar{10}$	97	−81	220	62	−88	011	95	−95
804	82	−117	6,0,$\bar{10}$	12	24	320	64	−22	013	51	−46
604	148	−127	8,0,$\bar{10}$	112	−121	420	7	−5	015	134	124
404	153	115	10,0,$\bar{10}$	122	−97	520	25	−26	017	33	29
204	88	−87	12,0,$\bar{10}$	11	−17	620	33	19	022	24	30
20$\bar{4}$	22	46	26,0,$\bar{10}$	44	65	720	14	−17	024	33	−36
40$\bar{4}$	294	−334	16,0,12	21	5	820	22	16	026	35	−24
60$\bar{4}$	272	−265	14,0,12	12	−6	920	16	14	033	35	42
80$\bar{4}$	26	26	12,0,12	14	23	10,2,0	24	−34	044	30	−14
10,0,$\bar{4}$	14	1	8,0,12	24	−37	11,2,0	10	−2	046	94	−110
14,0,$\bar{4}$	61	52	6,0,12	13	20	12,2,0	31	43	055	39	−8
16,0,$\bar{4}$	20	−48	2,0,$\bar{12}$	33	35	15,2,0	12	18	066	49	−7
18,0,$\bar{4}$	60	−68	4,0,$\bar{12}$	33	−57	18,2,0	66	75			
18,0,6	37	−37	8,0,$\bar{12}$	36	−5	19,2,0	29	30			

Except for the work carried out on the XRAC computer, most of the Fourier syntheses were evaluated numerically. For some of the difference syntheses a mechanical Fourier synthesizer was employed (Vand, *ibid.*, 1950, **27**, 257); others were calculated by numerical methods. In the structure-factor calculations, an empirical scattering curve for carbon was used (Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 106), without any allowance for hydrogen atoms. Owing to the large unit cell and the complex arrangement of atoms, most of the structure factors attain only a very small fraction of their possible maximum values. At first the value for the average discrepancy between calculated and observed structure factors (expressed as a sum of all the discrepancies divided by the total of the observed F values) was far from encouraging, but it improved steadily as the refinement proceeded. The structure factors

calculated from the final co-ordinates are given in Table 2 (F_c), and the overall discrepancy is 29%. For the ($h0l$) zone, which was most intensively studied, the value is 26·6%. In the ($hk0$) zone the reflections are mostly very weak, and here the discrepancy is about 40%. The ($0kl$) zone was not completely calculated, but the agreements found are reasonable. The above discrepancy figures are rather poor and indicate that considerable further refinement should be possible. This would be difficult to achieve, however, without a full three-dimensional investigation; at the present stage it may be concluded that the main outlines of the structure are well established, but that the individual atomic positions are subject to errors of between 0·1 and 0·2 Å.

We thank Professor J. W. Cook for the crystals used in this investigation and Professor R. Pepinsky of State College, Pennsylvania, for much help and the use of the XRAC computer in effecting some of the Fourier summations. Part of the work was done during the tenure of an I.C.I. Fellowship (V. V.) and of a Coats Fellowship (A. O. M.).

CHEMISTRY DEPARTMENT, THE UNIVERSITY, GLASGOW. [*Received, December 13th*, 1953.]

The Kinetics of Ionic Polymerisations. Part IV. The Action of Iodine Chloride and Iodine Bromide on* n-*Butyl Vinyl Ether.*

By D. D. ELEY and J. SAUNDERS.

[Reprint Order No. 4883.]

The polymerisation of *n*-butyl vinyl ether catalysed by iodine monochloride or iodine monobromide obeys third-order kinetics, as found earlier for iodine, but the apparent velocity constant for both interhalogen compounds is only 8 $l.^2$ $mole.^{-2}$ $min.^{-1}$ compared with 1800 for iodine. In the case of iodine monobromide, 15% of the observed catalytic velocity is probably due to iodine formed by decomposition, and the true velocity constants probably lie in the order $I_2 > ICl > IBr > Br_2$. These facts are discussed in relation to the halogen-addition reaction, and a mechanism involving a carbonium ion as a common intermediate is proposed.

THE polymerisation of 2-ethylhexyl vinyl ether catalysed by iodine was found to be of first order in monomer and of second order in iodine, and it was suggested that the first step involved the bimolecular ionisation of iodine to give I^+ and I^-_3 ions, the I^+ adding to the double bond of the monomer to give a reactive carbonium ion which entered into an ionic polymerisation chain-reaction (Parts I and II, Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425, 436). These kinetics held in light petroleum, diethyl ether, and ethylene dichloride, and subsequently were found valid for other vinyl ethers with the additional proviso that at high monomer concentrations the rate became of zero order in monomer, or even started to decrease. This latter behaviour was attributed to binding of iodine in a catalytically inactive π-complex with the double bond of the monomer (Part III, Eley and Saunders, *J.*, 1952, 4167).

Polymers isolated by pumping off monomer and solvents at 60° contained no iodine. At the end of a polymerisation run only 20—50% of the iodine added was titratable, the rest being bound in the polymer as di-iodide or π-complex, and dissociating therefrom at 60°. Bromine analysis showed rather less than one double bond per polymer molecule, which was attributed to some iodination of the "dead" polymer having occurred. Qualitative experiments in this laboratory by A. R. Richards (unpublished report, June 1947) had established that iodine monochloride and bromine acted as catalysts but gave a much slower rate than iodine. This is in contrast to the halogenation of allyl acetate in acetic acid, which follows the same third-order law with rate constants in the relative order: I_2 (1) $<$IBr (3×10^3) $<Br_2$ (10^4) $<$ICl (10^5) $<$BrCl (4×10^6) (White and Robertson, *J.*, 1939, 1509). It is therefore of great interest to investigate quantitatively the catalytic action of interhalogen compounds on the polymerisation of vinyl ether.

* Part III, *J.*, 1952, 4167.

Experimental

The technique used was that of Eley and Richards (*loc. cit.*), the polymerisations being followed in evacuated, sealed dilatometers at 25°. The dilatometers were opened at 30—40% polymerisation, and the reaction stopped by addition of excess of aqueous sodium thiosulphate, except in the case of the iodine bromide runs. Densities and cryoscopic molecular weights of all polymers were determined (Eley and Saunders, *loc. cit.*).

In runs with iodine bromide the reaction mixture at 30% polymerisation was titrated with sodium thiosulphate to determine "combined halogen." Specimens were analysed for total halogen commercially.

In all runs *n*-butyl vinyl ether was the monomer and diethyl ether the solvent, and these were purified as described in Part I (*loc. cit.*). Iodine monochloride and iodine monobromide

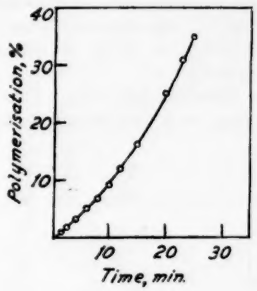
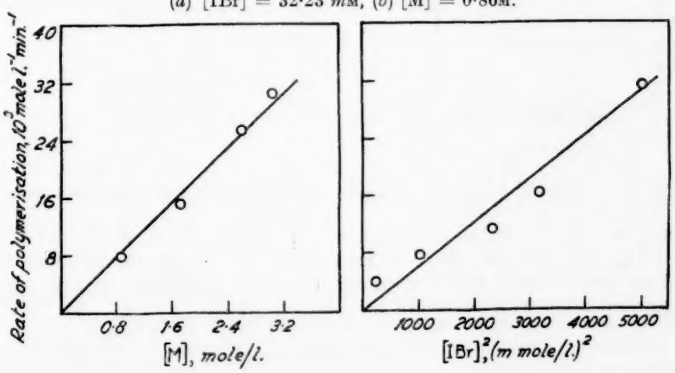


FIG. 1. *The time course of polymerisation catalysed by iodine bromide.* [M] = 0·86M. [C] = 32·23 mM.

FIG. 2. *Effect of catalyst and monomer concentrations on the initial rate with iodine bromide.* (*a*) [IBr] = 32·23 mM, (*b*) [M] = 0·86M.



were purified by two sublimations (Palmer and Wiig, *J. Amer. Chem. Soc.*, 1952, **74**, 2785), the second into evacuated bulbs which were sealed off for storage. Each bulb contained enough catalyst for two runs, and the ethereal catalyst solution was prepared freshly each day in nitrogen in a dry box. These iodine halides are sensitive to traces of moisture (Cornog and Karges, *J. Amer. Chem. Soc.*, 1932, **54**, 1882), and not only slowly decompose but also react with diethyl ether in both cases liberating iodine (Gillam and Morton, *Proc. Roy. Soc.*, 1931, *A*, **132**, 152; Gillam, *Trans. Faraday Soc.*, 1933, **29**, 1132), so that it is imperative to use fresh solutions.

Results

Reaction Velocity.—No induction periods were observed. With iodine monochloride the initial 2—10% of the polymerisation–time curve was linear, and then fell off as expected from mass-action considerations. The results were similar to those observed earlier with iodine. With iodine monobromide the initial linear period was followed by a gradual increase in velocity of polymerisation (Fig. 1), an effect which we have never found before.

The effects of catalyst and monomer concentration on the initial rate of polymerisation in the iodine monobromide case enables us to conclude that

$$-\mathrm{d[M]/dt_{initial}} = k[\mathrm{C}]^2[\mathrm{M}], \text{ and } k_{\mathrm{IBr}} = 8{\cdot}2 \text{ l.}^2 \text{ mole.}^{-2} \text{ min.}^{-1}.$$

[C] is the total concentration of iodine monobromide in the mixture. For iodine monochloride the rate was also proportional to [C]^2 but the effect of monomer concentration was not determined. The same kinetic law as for iodine monobromide being assumed, $k_{\mathrm{ICl}} = 8{\cdot}3$ l.^{2} mole^{-2} min.$^{-1}$.

The Iodine Bromide Polymers.—These were transparent mobile liquids varying from water-white to orange. The densities (d_4^{25}) varied from 0·9056 to 0·9562, an average for all polymers being 0·9321. In the series of runs recorded in Fig. 2 the products at 30% polymerisation contained 53·3 to 76·6% of the initial catalyst concentration as " combined halogen " as determined by titration. The molecular weights varied from 300 to 850 in no systematic fashion. The *total halogen* in a polymer of molecular weight (M) 650 was 5·69%, and in one of M 350 was 1·9%, as determined by microanalysis. The first figure corresponds to 2I/7 chains or 1Br/2 chains and the second to 1I/19 chains or 1Br/12 chains. The halogens were not distinguished in the microanalyses.

The Iodine Chloride Polymers.—These were transparent yellow to orange, mobile liquids, of density varying from 0·9348 to 0·9849, the average for all specimens being 0·9618.

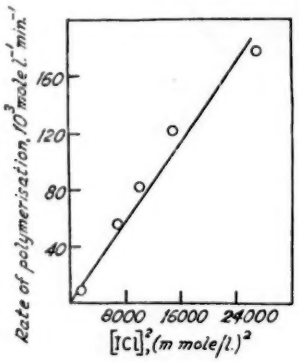


FIG. 3. *Effect of catalyst concentration on the initial rate with iodine chloride.* [M] = 0·86M.

Two polymer specimens had M 350 and 650, and the latter gave on microanalysis 9·4% of halogen, *i.e.*, 1I/2 chains or 5Cl/3 chains.

In two cases the polymers deposited a yellow crystalline sediment, which had m. p. 100—110° [Found : C, 5·0% ; H, 0·4% (Mr. B. S. Noyes, Bristol]. Insufficient was available for halogen analysis. These data suggest that the compound was iodoform, m. p. 119° (Calc. : C, 3·05 : H, 0·26%), contaminated with polymer.

DISCUSSION

The Velocity.—The iodine monochloride and iodine monobromide polymerisations have kinetics identical with those of the iodine polymerisation of *n*-butyl vinyl ether (Eley and Saunders, *loc. cit.*) but the third-order velocity constant of about 8 for the first two catalysts is to be compared with a value of 1800 for iodine. Now, a certain amount of iodine is present even in fresh iodine halide solutions, formed by the dissociation $3\mathrm{IX} \rightleftharpoons \mathrm{I_2} + \mathrm{IX_3}$. At 25° the chloride is 0·42% decomposed (Cornog and Karges, *loc. cit.*) and the bromide 8% in the vapour phase and 9·5% in carbon tetrachloride solution (Yost, Anderson, and Skoog, *J. Amer. Chem. Soc.*, 1933, **55**, 552). If these figures apply to the ethereal solution we expect catalysis due to the free iodine, the apparent rate constants being given by $[\mathrm{I_2}]^2 \times 1800 = (1{\cdot}4 \times 10^{-3})^2 \times 1800 = 0{\cdot}00353$ for iodine chloride and $(0{\cdot}0267)^2 \times 1800 = 1{\cdot}28$ for iodine bromide. It is clear that the value of 8·3 observed for the iodine chloride is 2350 times greater than the value estimated on a basis of catalysis by its free-iodine content, and we therefore attribute this catalysis to the iodine monochloride itself. On the other hand the value for iodine monobromide is only 6·4 times the estimated rate for the free iodine present, so that about 85% of the reaction rate is due

to iodine bromide and 15% to the free iodine. Furthermore, the reaction velocity increases with time in this case only, which strongly suggests the iodine monobromide to be decomposing as polymerisation proceeds. We therefore conclude that the true third-order constant for iodine monobromide is less than 8·2, so that $k_{I_2} = 1800 > k_{ICl} = 8{\cdot}3 > k_{IBr} \sim 7 > k_{Br_2}$ is the order of decreasing catalytic activity. Since bromine in carbon tetrachloride may be used quantitatively to brominate the double bond of monomeric vinyl 2-ethylhexyl ether (Richards, unpublished) we may conclude that this is an even less active catalyst for polymerisation than iodine monobromide.

The Polymers.—The average degree of polymerisation (D.P.) of the polymer produced by iodine monobromide and iodine monochloride of 5·2 is rather less than the value of 9·8 found earlier for iodine, but the factor of 2 may be neglected compared with the factor of 220 found for the overall velocities of polymerisation. Thus, since the material chains in these cases are ended by transfer (Eley and Richards, *loc. cit.*) we may suppose the ratio of propagation rate to transfer rate to be hardly affected by the catalyst, and the difference in overall velocity to be due to differences in the initiation steps.

It is believed that the halogen in the product has arisen from an attack by the catalyst on the double bond of the dead polymer. The interhalogen compounds are much more efficient in the addition reaction than iodine, which explains why no halogen was found in the latter case (Eley and Richards, Eley and Saunders, *locc. cit.*).

The Kinetic Scheme.—It is instructive to discuss the problem of halogen addition as well as polymerisation in the light of the kinetic scheme advanced in Parts I and II (*locc. cit.*) for this polymerisation :

$$2IX \rightleftharpoons I^+ + IX_2^-\ ;\ k_1,\ k_{-1},\ K_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$I^+ + M \rightleftharpoons I^+M,\ k_2,\ k_{-2},\ K_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$\left.\begin{aligned} I^+M + M &\longrightarrow M_2^+ \\ M_{n-1}^+ + M &\longrightarrow M_n^+ \end{aligned}\right\} k_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$M_n^+ \longrightarrow M_n\ ;\ k_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$M_n^+ + M \longrightarrow M_n + M^+\ ;\ k_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

(where, *e.g.*, k_1 is the constant of the forward reaction, k_{-1} that of the reverse reaction, and K_1 the equilibrium constant).

In order to do this we need to consider the reverse reactions in steps (1) and (2) in addition to the forward constants usually considered. Now, polymerisation is very rapid, *i.e.*, $k_3 \gg k_1,\ k_2$, and the usual analysis holds :

$$-\mathrm{d[M]}/\mathrm{d}t = k_1k_3[\mathrm{IX}]_f^2[\mathrm{M}]/k_4 \qquad \text{D.P.} = k_3[\mathrm{M}]/(k_4 + k_5[\mathrm{M}])$$

where $[IX]_f$ is the concentration of free iodine or interhalogen *i.e.*, the total concentration less that bound as inactive complex with the double bond. While it is possible that, for a given total concentration of catalyst, $[ICl]_f < [I_2]_f$ because of the formation of a stronger inactive complex, this can hardly affect the velocity by a factor smaller than 0·5 [cf. values for benzene derivatives (Andrews and Keefer, *J. Amer. Chem. Soc.*, 1950, **72**, 5170; 1952, **74**, 4500)]. Therefore we conclude that the results for the overall velocity are due to a decrease of k_1 over the series $I_2 > ICl > IBr$.

We now consider whether halogenation might follow the same route to I^+M, in the case of a monomer unreactive to polymerisation :

$$I^+M + IX_2^- \longrightarrow IMX + IX\ ;\ k_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The overall velocity constants for halogenation of allyl acetate are much less than for polymerisation of *n*-butyl vinyl ether. Thus for iodine monochloride with allyl acetate in acetic acid $k = 0{\cdot}045$ l.^{2} mole^{-2} min.$^{-1}$ (White and Robertson, *loc. cit.*) which is 200 times *slower* than the above polymerisation. The addition of iodine to allyl acetate is 10^5 times slower than the previous value, and therefore 4×10^9 times slower than the polymerisation of *n*-butyl vinyl ether by iodine. So allyl acetate is a much less reactive monomer than *n*-butyl vinyl ether, k_3 being negligible (no polymerisation). It should also be possible to

assume k_{-1}, $k_{-2} \gg k_6$, whereupon the kinetics of halogenation become $-\mathrm{d}[IX]/\mathrm{d}t = k_6[I^+M][IX_2^-] = k_6K_1K_2[IX]^2[M]$ as found experimentally. We should expect k_6 to increase with decreasing stability of the IX_2^- ion, which for varying X is I > Br > Cl (Sidgwick, "The Chemical Elements and Their Compounds," II, 1193) and this result is also that found experimentally.

It may be remarked that White and Robertson favoured a two-stage process:

$$M + Br_2 \rightleftharpoons MBr_2$$
$$MBr_2 + Br_2 \longrightarrow \text{products}$$

and this would be a mechanism quite distinct from polymerisation, and indeed it might be argued from our results that as polymerisation shows such different behaviour from halogenation, the latter can scarcely involve the same active carbonium ion as intermediate. However, it has been shown that halogenation kinetics may be reconciled with the carbonium ion intermediate. De la Mare's argument (*Quart. Reviews*, 1949, **3**, 133) against a pre-equilibrium of the form (1) in the case of bromination is that "addition of negative ions would greatly reduce the rate of addition (*e.g.*, $Br^+ + OAc^- \rightleftharpoons BrOAc$)." However, the only negative ion that could reduce the concentration of Br^+ produced by an equilibrium (1) would be Br_3^- and the appropriate test, which we hope to make later, would be to add $CsBr_3$ or $RbBr_3$.

THE UNIVERSITY, BRISTOL. [*Received, December 12th*, 1953.]

The Kinetics of Ionic Polymerisations. Part V. The Inhibition by Pyridine and 2-Iodopyridine of Polymerisation of* n*-Butyl Vinyl Ether Catalysed by Iodine.*

By D. D. ELEY and J. SAUNDERS.

[Reprint Order No. 4884.]

The polymerisation of *n*-butyl vinyl ether catalysed by iodine is inhibited by pyridine and 2-iodopyridine. The results may be described in terms of a ternary 1 : 1 : 1-complex, and a number of these complexes have been prepared. The formation equilibrium constants are deduced from the kinetics of inhibition and a structure is postulated.

True velocity constants for the polymerisation of the different vinyl ethers have been calculated from the apparent velocity constants quoted in Part III, and the values of the iodine–vinyl ether complex formation constant K_c have been revised. These data are given in an Appendix.

THE initiation of vinyl ether polymerisation by iodine has been attributed to the unstable I^+ ion reacting with the double bond to form a carbonium ion (Part I, Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425). If this is so we should expect the addition of pyridine to inhibit the initiation step by forming a PyI^+ ion. While co-ordination of this type serves to stabilise the iodine cation (cf. Sidgwick, "The Chemical Elements and Their Compounds," 1950, Vol. II, p. 1241) it will at the same time be expected to destroy its activity as an electrophilic catalyst. Here we study the subject quantitatively, both with pyridine and with 2-iodopyridine which we expect to be a somewhat weaker electron donor than pyridine itself.

EXPERIMENTAL

The monomer used was *n*-butyl vinyl ether, the catalyst iodine, and the solvent diethyl ether. These materials were purified as described in Part I (*loc. cit.*). The polymerisations were followed in dilatometers at 25°.

* Part IV, preceding paper.

" AnalaR " pyridine was first dried (KOH, then P_2O_5), and then distilled twice *in vacuo*; it had $d_4^{25} = 0{\cdot}971$, $n_D^{21{\cdot}5} = 1{\cdot}5046$, and was used as a solution in diethyl ether.

2-Iodopyridine was kindly supplied by Professor Wilson Baker and Dr. R. F. Curtis. It was purified by repeated distillation *in vacuo*, giving a colourless product, $d_4^{25} = 1{\cdot}928$ g./c.c., $n_D^{20{\cdot}5} = 1{\cdot}6242$. It was used in ethereal solution.

Results

The results of the kinetic investigations are shown in Table 1 and Fig. 1. It is noteworthy that with 2-iodopyridine a small amount of the base actually increased the rate of reaction by about 25%. When pyridine was used there was evidence for the formation of small amounts of an orange-brown deposit or red crystals in the reaction mixture. With 2-iodopyridine a yellow-orange cloudiness developed in the mixture at 25°, but redissolved without leaving any solid deposit. In some experiments with iodine, *cyclo*hexyl vinyl ether, and pyridine, a transparent red liquid was formed at 0°, and when the temperature was raised a deep red crystalline sediment was obtained, insoluble in distilled water and diethyl ether but soluble in alcohol. It was decomposed by aqueous sodium thiosulphate and gave a positive starch–iodide test.

As a result of these observations the formation of crystalline complexes at room temperature in the system pyridine–iodine–X was examined, where X was a vinyl ether or other compound.

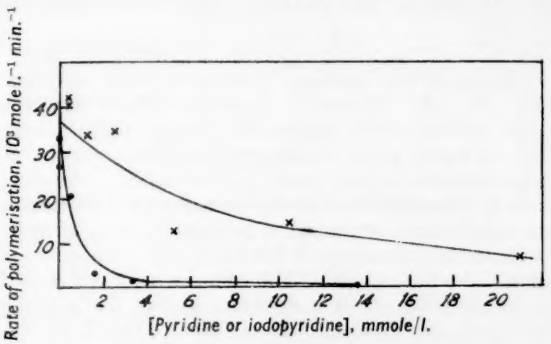


FIG. 1. *The rate of polymerisation of* n-*butyl vinyl ether in the presence of pyridine (full circles) and 2-iodopyridine (crosses). The lines are calculated from the theory.*

Preparation of Complexes.—The reactant X was added to the red-brown solution of iodine in pyridine, with the results shown. All these components were necessary for *complex* formation. The calculated analytical figures are for 1 : 1 : 1–I_2 : pyridine : X.

X = n-*Butyl vinyl ether.* A deep red oil was formed which crystallised as a grey-brown solid, insoluble in diethyl ether and stable up to 40—50°.

X = cyclo*Hexyl vinyl ether plus diethyl ether.* Red needles and a little red oil were formed. The complex was insoluble in ether, but soluble in pyridine and alcohol. It was stable if separated, but liquefied after a few days if kept in contact with supernatant liquor.

X = cyclo*Hexyl vinyl ether.* Pale yellow needles and red microcrystals were formed, which changed to a viscous red oil if kept in contact with supernatant liquor. The crystals were soluble in pyridine, chloroform, and nitrobenzene.

X = 2-*Ethylhexyl vinyl ether.* A red oil was formed which slowly gave chocolate-coloured crystals, insoluble in ethyl ether, and melting with decomposition at 30° with liberation of iodine. The complex gave conducting solutions in acetone and pyridine, the specific conductance of the almost saturated solution being respectively $3{\cdot}2 \times 10^{-4}$ and $1{\cdot}5 \times 10^{-4}$ mho, at 18°.

X = *Ethyl vinyl ether.* A yellow oil was formed which became red and gave pale grey crystals, insoluble in ethyl ether, but soluble in pyridine, acetone, etc. They were stable to 40—50° (Found : C, 27·65; H, 3·3; I, 60·35; N, 4·1; O, 4·6. Required : C, 26·7; H, 3·2; I, 62·7; N, 3·5; O, 3·93%).

X = iso*Butyl vinyl ether.* A deep red oil was formed, slowly crystallising to a deep red solid, insoluble in ethyl ether.

X = 2-*Chloroethyl vinyl ether.* A red oil was formed together with pale yellow crystals. This complex was formed more slowly than with the other vinyl ethers (Found : C, 25·5; H, 3·35; Hal, 60·8; N, 3·0. Required : C, 24·6; H, 2·7; Hal, 65·9; N, 3·2%).

X = *Divinyl ether.* A red oil was formed, crystallising as a pale yellow transparent solid, insoluble in ethyl ether and non-polar solvents, but soluble in polar solvents (Found : C, 27·5; H, 3·0; I, 61·9; N, 4·1. Required : C, 26·8; H, 2·7; I, 63·0; N, 3·5%).

X = *Acrylonitrile.* Chocolate-brown prismatic crystals were slowly formed, but no oil. It was noticed that the crystal habit was different from that of the vinyl ether complexes (Found : C, 25·2; H, 2·0; N, 6·8. Required : C, 24·9; H, 2·1; N, 7·25%).

X = *α-Methylstyrene.* The complex was a red oil, giving no crystals, and was only slowly formed in the presence of excess of monomer. It was sparingly soluble in diethyl ether, and soluble in alcohol.

X = *Diethyl ether.* A little red oil was observed, which was only formed if ether was present in excess.

X = *Dibutyl ether.* Some red oil was formed, but only in the presence of excess of ether.

X = *Anisole.* No complex was obtained.

X = *Water.* A large yield of orange crystals was obtained which were soluble in pyridine and very soluble in ethyl ether.

Apart from the acrylonitrile complex which was stable all the above complexes showed appreciable decomposition after 5 months' storage in stoppered tubes in the dark. The colour darkened and an odour developed which in a number of cases appeared to be that of the alcohol corresponding to the side-chain in the ether, *e.g.*, *cyclo*hexyl vinyl ether (odour of *cyclo*hexanol). The *cyclo*hexyl vinyl ether complex after storage had C, 26·2; H, 2·9%.

Discussion

Nature of the Complex.—The above work supports the notion that the complexes are $1Py : 1I_2 : 1X$. Where X is a vinyl ether, acrylonitrile, or α-methylstyrene relatively stable yellow or red needles are formed which decompose at 40—50°, and are probably ionic or highly polar as they are insoluble in ether and non-polar solvents, and dissolve in polar solvents to give conducting solutions. The complexes where X is a saturated ether seem to be much more slowly formed, and if an electron-attracting group is present in the saturated ether, as phenyl in anisole, no complex is formed at all. We take these results to mean that formation of the vinyl ether complex occurs through the olefinic group rather than the ether oxygen. The complex with water is obviously of a different type, and is probably similar to that described as PyI_2 by Waentig (*Z. physikal. Chem.*, 1909, **68**, 513) and Py_2I_2 by Chatelet (*Ann. Chim.*, 1934, **2**, 5; *Compt. rend.*, 1933, **196**, 1421, 1607). A range of complexes containing positive iodine, $Py_2I^+X^-$; PyI^+X^- and related complexes, have been prepared by Carlsohn (*Ber.*, 1935, **68**, 2209; *Angew. Chem.*, 1933, **46**, 747) and recently by Zingaro, Goodrich, Kleinberg, and VanderWerf (*J. Amer. Chem. Soc.*, 1949, **71**, 575; 1950, **72**, 5341). Here X is an acid radical, such as nitrate, acetate, etc., but in our complexes the third component is monomer. For iodine–pyridine solutions, conductivity (Audrieth and Birr, *J. Amer. Chem. Soc.*, 1933, **55**, 668), polarisation (Fairbrother, *J.*, 1948, 1051), and calorimetric studies (Markley and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 621) suggest the formation of salts or ion pairs of the form $PyI^+ I^-$. Very recently Zingaro, VanderWerf, and Kleinberg, from absorption spectra and exchange with radio-iodine (*J. Amer. Chem. Soc.*, 1951, **73**, 88, 1865), postulated an equilibrium :

$$2I_2 + Py \rightleftharpoons PyI^+ + I_3^-$$

These considerations suggest that our complexes may probably be formulated as $(Py\ X\ I)^+\ I^-$, and the results further suggest that in vinyl ethers the double bond rather than the ether group is involved, *e.g.*

$$\left\{Py \longrightarrow I \ldots \begin{matrix} CH_2 \\ \| \\ CH_2\text{–}OR \end{matrix}\right\}^+ I^-$$

The bond between ethylene and the iodine atom is unlikely to be a donor link of the π electrons, since it is improbable that the empty 5*d* or 6*s* shell of the iodine atom will accept electrons in this way (the 5*p* shell is already completed by the electron pair from the nitrogen atom). Also, such a bond would involve a large accumulation of electrons on the iodine atom. Finally the formation of the complexes is not inhibited by the presence of electron-attracting side groups on the vinyl ether, chlorovinyl ether and divinyl ether

both giving complexes. A possible bond involves a donation of electrons from the complete 4*d* shell of the iodine atom to the empty antibonding π orbital of the ethylenic complex, as suggested by Dewar for Ag^+ and Br^+ (*Bull. Soc. chim.*, 1951, **18**, *C*79). Such a link might serve to stabilise the N→I bond by transferring electron density from the iodine atom to the ethylenic compound. It would not be expected to activate the double bond for polymerisation (Eley, " Cationic Polymerisation and Related Complexes," Cambridge, 1953, p. 67, Ed. Plesch). The relationship of these complexes to the binary complexes of iodine and ethylenic substances (Andrews and Keefer, *J. Amer. Chem. Soc.*, 1952, **74**, 458; Freed and Sancier, *ibid.*, p. 1273; Ketelaar and Van der Stolpe, *Rec. Trav. chim.*, 1952, **71**, 805) requires further investigation.

The Kinetics.—The above results suggest we are concerned with a ternary equilibrium of iodine, pyridine, and monomer to give inactive complex :

$$\underset{[I_2]-x-y}{I_2} + \underset{[Py]}{Py} + \underset{[M]}{M} \rightleftharpoons \underset{y}{I_2PyM}$$

In addition there is the previously postulated equilibrium between iodine and monomer to give inactive complex :

$$\underset{[I_2]-x-y}{I_2} + \underset{[M]}{M} \rightleftharpoons \underset{x}{I_2M}$$

We define $K_p = \dfrac{y}{([I_2]-x-y)[Py]\,.\,[M]}$ and $K_c = \dfrac{x}{([I_2]-x-y)[M]}$

and deduce the concentration of free unbound iodine to be

$$[I_2]_f = \frac{[I_2]}{1 + K_c[M] + K_p[Py][M]} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The easiest procedure is to assume the kinetic expression with a true velocity constant k_t,

$$-d[M]/dt = k_t[I_2]_f^2[M]$$

then $k_t = 4000$ l.^{2} mole^{-2} min.$^{-1}$ (see appendix)

From this equation we can calculate $[I_2]_f$ for the measured rates, at the given monomer concentration $[M] = 0{\cdot}86$ mole l.$^{-1}$. A plot of $1/[I_2]_f$ against the concentration of pyridine should give a straight line, since from equation (1)

$$\frac{1}{[I_2]_f} = \frac{1 + K_c[M]}{[I_2]} + \frac{K_p[M]\,.\,[Py]}{[I_2]}$$

Values of K_p so derived are: pyridine, $K_p = 1{\cdot}9 \times 10^3$ l.^{2} mole^{-2}; 2-iodopyridine, $K_p \sim 100$ l.^{2} mole^{-2}.

The point at the highest pyridine concentration is neglected. It lies off the line and the experimental error will have a large effect for such a very small

TABLE 1.

Inhibition by pyridine. [M] = 0·86 mole/l.; $[I_2] = 4{\cdot}37$ mmole/l. at 25°.

IPy, mmole/l.	Rate (obs.) mole l^{-1}. min^{-1}. $\times 10^3$	Rate (calc.) mole l^{-1}. min^{-1}. $\times 10^3$
0	27·3	36·7
0	33·1	36·7
0·546	20·4	13·2
1·638	3·6	4·1
3·277	1·6	1·5
13·66	0·4	0·12

Inhibition by 2-iodopyridine. [M] = 0·86 mole/l.; $[I_2] = 4{\cdot}37$ mmole/l. at 25°.

IPy, mmole/l.	Rate (obs.) mole l^{-1}. min^{-1}. $\times 10^3$	Rate (calc.) mole l^{-1}. min^{-1}. $\times 10^3$
0·418	40·8	34·6
0·418	42·0	34·6
1·254	33·9	31·3
2·508	35·0	27·0
5·238	13·0	20·5
10·48	14·3	13·1
20·95	6·6	6·6

reaction rate. For 2-iodopyridine it is necessary to neglect the four points at the lowest concentrations, as here the reaction velocity is *increased*. This effect, however, is well outside the experimental error. It cannot arise from iodine impurity in the iodopyridine since this was carefully removed, and the effect has not so far been explained. To compare

theory with experiment it is convenient to recalculate values of the reaction velocity as a function of pyridine concentration:

$$-\frac{d[M]}{dt} = k_t[I_2]_f^2[M] = \frac{k_t}{(1 + K_c[M] + K_p[Py][M])^2}[I_2]^2[M]$$

We take $k_t = 4000$ l.^{2} mole^{-2} min.$^{-1}$, $K_c = 0{\cdot}4$ l. mole^{-1}, $K_p = 1{\cdot}9 \times 10^3$ l.^{2} mole^{-2}, and obtain the figures given in the last column of Table 1, and the full curve in Fig. 1. Figures are also shown for 2-iodopyridine, calcuiated with the above data and the value $K_p = 100$ l.^{2} mole^{-2}.

Appendix

In Part III (*loc. cit.*) values of the apparent third-order constant k at *low* monomer concentrations, and K_c are listed. We now require the true velocity constants k_t which refer to the concentration of free iodine:

$$v = k_t[I]_f^2[M] = \frac{k_t[I_2]^2[M]}{(1 + K_c[M])^2}$$

and we have calculated these by fitting the theoretical formula to the experimental points over the whole range of monomer concentrations. Examples are given in Fig. 2 (*n*-butyl

Fig. 2. *Experimental points and theoretical curve* ($k_t = 4000$, $K_c = 0{\cdot}4$) *for* n-*butyl vinyl ether.*

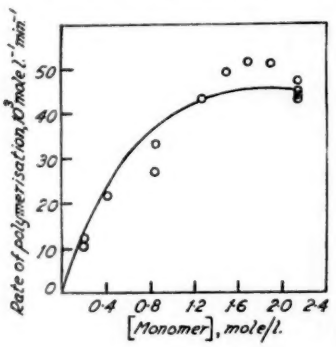
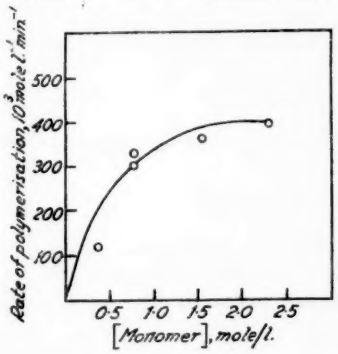


Fig. 3. *Experimental points and theoretical curve* ($k_t = 40{,}000$, $K_c = 0{\cdot}5$) *for* cyclo*hexyl vinyl ether.*



vinyl ether) and Fig. 3 (*cyclo*hexyl vinyl ether), the solid lines being calculated by using the new k_t and K_c values in Table 2. There are noticeable deviations between the theoretical curve and the experimental points, part of which may be experimental error,

Table 2. *Kinetic constants for vinyl ether polymerisations.*

Monomer	k (Part III)	k_t (new)	K_c (Part III)	K_c (new)
	l.^{2} mole^{-2} min.$^{-1}$		l. mole^{-1}	
*cyclo*Hexyl	22,000	40,000	1·25	0·5
*iso*Butyl	1,900	4,000	1·25	0·8
2-Ethylhexyl	1,000	2,000	0·67	0·4
n-Butyl	1,800	4,000	0·5	0·4
Ethyl	1,900	5,000	0·31	0·31
2-Chloroethyl	90	125	<0·23	0·05

but part may be attributed to shortcomings in the theory: *e.g.*, neglect of activity coefficients in the equilibrium equations. The tendency is for the experimental points to rise more gradually and then turn over rather more abruptly than the theoretical curve at high concentrations, at least for the case of Fig. 2, and also for the *iso*butyl and 2-ethylhexyl ethers. The new values for k_t and K_c are given in Table 2 together with the values deduced for the apparent velocity constants k and K in the previous paper.

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The Kinetics of Ionic Polymerisations. Part VI. The Copolymerisation of isoButyl Vinyl Ether and 2-Chloroethyl Vinyl Ether.*

By D. D. Eley and J. Saunders.

[Reprint Order No. 4885.]

The copolymerisation of *iso*butyl vinyl ether and 2-chloroethyl vinyl ether catalysed by iodine obeys Mayo and Walling's copolymerisation equation. The reactivity ratios are respectively 1·90 and 0·70. Third-order kinetics are obeyed with an apparent velocity constant in between those for the two monomers, but nearer the slower one (2-chloroethyl vinyl ether). An attempt has been made to describe the effect of monomer concentration on rate in terms of the true velocity constants for the separate monomers and the individual formation constants K_c for the inactive iodine–monomer complexes. The results suggest that the K_c value of the *iso*butyl vinyl ether is diminished in the presence of 2-chloroethyl vinyl ether. This may be a dielectric-constant effect. Evidence for this view is also found in the absence of a maximum in the curve of rate against total monomer concentration.

Copolymerisation has been reviewed by Mayo and Walling (*Chem. Reviews*, 1950, **46**, 191) and it appears that quantitative information for carbonium ion copolymerisation is sparse compared with that available for radical intermediates. There are no data for the "reactivity ratios" of the vinyl ethers, and here we make a fairly complete investigation of one monomer pair, catalysed by iodine in the solvent diethyl ether. There is also considerable interest in comparison of kinetics of the copolymerisation with those to be expected from the polymerisation of the individual monomers.

Experimental

The polymerisations were followed in the usual dilatometer (see preceding papers) at 25°. The solvent used was diethyl ether, and the iodine catalyst was used at a concentration of 4·37 mmole/l. in all cases. The materials were all purified as previously described (Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 425). The rate of reaction was determined on the basis of the volume contraction, calculated from the density of the mixed monomer system, and the isolated polymer. The monomer contents of the copolymers were determined from commercial halogen microanalyses. Thus density and halogen content were determined for all polymers, and cryoscopic molecular weights in one or two cases.

Results

Effect of Monomer Concentration on Rate.—A number of runs were made in which the total monomer concentration was varied, the molar ratio constant being kept at 43·9 mole % of *iso*butyl vinyl ether to 56·1 mole % of 2-chloroethyl vinyl ether. The catalyst concentration was 4·37 mmole/l. The results are shown in Fig. 1.

It is apparent that the reaction is of first order in monomer up to 4 mole/l., and shows no marked falling off. By assuming that a third-order equation holds, k = velocity/[M][C]^2 is found to have the value 131 l.^{2} mole^{-2} min.$^{-1}$.

The polymers varied somewhat in properties, being liquids, sometimes viscous, from yellow to orange and deep brown. The densities were in the range 0·9919 to 1·057, the average value for the six specimens being $d_4^{25} = 1·018$ (a mixture of 43·9 mole % of *iso*butyl vinyl ether and 56·1 mole % of 2-chloroethylvinyl ether has $d_4^{25} = 0·9015$).

Monomer Reactivity Ratios.—If $d[M_2]/d[M_1]$ be the relative rates of incorporation of monomer M_2 (2-chloroethyl vinyl ether) and monomer M_1 (*iso*butyl vinyl ether) in the polymer, for a ratio of monomer concentrations of $[M_1]/[M_2]$, then the reactivity ratio, r_2, is related to the reactivity ratio, r_1 (Mayo and Walling, *loc. cit.*), by the differential equation

$$r_2 = \frac{[M]_1}{[M_2]} \cdot \frac{d[M_2]}{d[M_1]} + \left(\frac{[M_1]}{[M_2]}\right)^2 \frac{d[M_2]}{d[M_1]} \cdot r_1 - \frac{[M_1]}{[M_2]}$$

* Part V, preceding paper.

For appreciable amounts of reaction it is more correct to use the integrated equation (Mayo and Walling, *loc. cit.*). The data in Table 1 have been analysed by both the integral and differential equations, by the usual graphical method of Mayo and Walling, with the results given below. As expected, the integral equation gives a slightly smaller error than the differential equation.

Differential equation,	*Integral equation,*
$r_1 = 1{\cdot}95 \pm 0{\cdot}1$	$r_1 = 1{\cdot}90 \pm 0{\cdot}05$
$r_2 = 0{\cdot}70 \pm 0{\cdot}1$	$r_2 = 0{\cdot}70 \pm 0{\cdot}05$

TABLE 1. *Composition (mole %) of monomer (initial) and copolymer.*

Monomer, M_1	20·7	43·9	61·05	70·15	91·25
M_2	79·3	56·1	38·95	29·85	8·75
Copolymer, M_1	31·45	61·7	72·8	82·15	95·0
M_2	68·55	38·3	27·2	17·85	5·0

Monomer Composition and Rate.—The relationship between monomer composition and overall rate was determined for a total monomer concentration of 4·1 mole/l. and catalyst concentration of 4·37 mmole/l. The values for the pure monomer are based on the data in Part III (*J.*, 1952, 4167), that for 2-chloroethyl vinyl ether (M_2) being interpolated, and that for butyl vinyl ether (M_1) being calculated from the equation given in the Appendix to Part V (preceding paper).

$$-\frac{d[M]}{dt} = \frac{k[I_2]^2[M]}{(1 + K_c[M])^2} = \frac{4000[I_2]^2[M]}{(1 + 0{\cdot}8[M])^2}$$

TABLE 2.

Monomer, mole %, M_1	0	20·7	20·7	43·9
M_2	100	79·3	79·3	56·1
Velocity, mole $l.^{-1}$ $min.^{-1}$	$6{\cdot}7 \times 10^{-3}$	$2{\cdot}42 \times 10^{-2}$	$3{\cdot}38 \times 10^{-3}$	$10{\cdot}26 \times 10^{-3}$
Monomer, mole %, M_1	70·15	91·25	100	
M_2	29·85	8·75	0	
Velocity, mole $l.^{-1}$ $min.^{-1}$	$17{\cdot}8 \times 10^{-3}$	$24{\cdot}37 \times 10^{-3}$	$17{\cdot}00 \times 10^{-3}$	

Degree of Polymerisation.—This was determined for two copolymers as 3·5 and 4·5. These values are rather lower than that expected for pure *iso*butyl vinyl ether polymer, of about 10, but similar to that expected for pure 2-chloroethyl vinyl ether polymer, of 4·6.

DISCUSSION

The true velocity constants k_t for the pure monomers were 4000 for *iso*butyl vinyl ether and 125 for 2-chloroethyl vinyl ether, and these constants involve the ratio of propagation to termination rates. On the other hand, the reactivity ratios of 1·9 for *iso*butyl vinyl ether and 0·7 for 2-chloroethyl vinyl ether which involve only the propagation rates are relatively much less different. This leads to the conclusion that the termination rate constants must be very different for the two monomers, *i.e.*, much less for the *iso*butyl than for the 2-chloro-ethyl ether.

It is also of considerable interest that the apparent copolymerisation velocity constant of 131 lies much nearer the figure 125 for 2-chloroethyl than 4000 for *iso*butyl vinyl ether. This again leads to conclusions about the termination step, and suggests that the copolymerisation kinetic chains preferentially end on a 2-chloroethyl vinyl ether monomer. The fundamental step may be loss of an I^+ ion and this would be expected to occur more easily with the 2-chloroethyl monomer than the *iso*butyl vinyl ether monomer, from considerations of the inductive effect of the side-group.

We can discuss the effect of monomer ratio on rate in terms of r_1, r_2, $k_{t,1}$ and $k_{t,2}$, if we extend the usual copolymerisation scheme to include inactive complexes. The steps are *

* Our usual numbering of velocity constants is altered so as to agree with that usually used in the field of copolymerisation.

Catalyst	$I_2 + I_2 \longrightarrow I^+ + I_3^-$, k_0
Initiation	$I^+ + M_1 \longrightarrow M_1^x$, k_1
	$I^+ + M_2 \longrightarrow M_2^x$, k_2
Propagation	$M_1^x + M_1 \longrightarrow M_{11}^x$, k_{11}
	$M_1^x + M_2 \longrightarrow M_{12}^x$, k_{12}
	$M_2^x + M_1 \longrightarrow M_{21}^x$, k_{21}
	$M_2^x + M_2 \longrightarrow M_{22}$, k_{22}
Transfer	$M_{1n}^x + M_1 \longrightarrow M_{1n} + M_1^x$, k_{311}
	$M_{1n}^x + M_2 \longrightarrow M_{1n} + M_2^x$, k_{312}
	$M_{2n}^x + M_2 \longrightarrow M_{2n} + M_2^x$, k_{322}
	$M_{2n}^x + M_1 \longrightarrow M_{2n} + M_1^x$, k_{321}
Termination	$M_{1n}^x \longrightarrow M_{1n}$, k_{41}
	$M_{2n}^x \longrightarrow M_{2n}$, k_{42}

The following data are known :

$$r_1 = k_{11}/k_{12} = 1{\cdot}9 \qquad r_2 = k_{22}/k_{21} = 0{\cdot}7$$

$$k_{t,1} = \frac{k_0 k_{11}}{k_{41}} = 4000 \qquad k_{t,2} = \frac{k_0 k_{22}}{k_{42}} = 125 \text{ (Appendix, preceding paper)}$$

Stationary concentrations of all intermediates being assumed, we can show that

$$-\frac{\mathrm{d}([M_1] + [M_2])}{\mathrm{d}t} = \frac{(r_1[M_1]^2 + 2[M_1][M_2] + r_2[M_2]^2)}{r_1 \frac{k_{41}}{k_0 k_{11}}[M_1] + r_2 \frac{k_{42}}{k_0 k_{22}}[M_2]}[I_2]_f^2$$

$$= \frac{(1{\cdot}9[M_1]^2 + 2[M_1][M_2] + 0{\cdot}7[M_2]^2)}{0{\cdot}475[M_1] + 5{\cdot}6[M_2]} 10^3 \,.\, [I_2]_f^2$$

$$= 10^3 A \,.\, [I_2]_f^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Now it can easily be shown, if K_{c1} and K_{c2} are the equilibrium constants for formation of inactive iodine-monomer complexes :

$$I_2 + M_1 \rightleftharpoons I_2M_1 \text{ and } I_2 + M_2 \rightleftharpoons I_2M_2$$

that
$$[I_2]_f = \frac{[I_2]}{1 + [M_1]K_{c1} + [M_2]K_{c2}} = \frac{4{\cdot}37 \times 10^{-3}}{1 + 0{\cdot}8[M_1] + 0{\cdot}05[M_2]} \quad . \quad . \quad . \quad (2)$$

Values of $[I_2]_f$ calculated from equation (2) are substituted in equation (1) to allow calculation of overall velocities of polymerisation. The values of 10^3A and $[I_2]_f$ are listed in Table 3.

TABLE 3. *Monomer composition–rate curve.* $[I_2] = 4{\cdot}37$ mmole/l. $[M_1] + [M_2] = 4{\cdot}1$ mole/l.

Monomer, %				$10^3 \times$ rate		Monomer, %				$10^3 \times$ rate	
$[M_1]$	$[M_2]$	10^3A	$[I_2]_f^2\ 10^6$	Calc.	Obs.	$[M_1]$	$[M_2]$	10^3A	$[I_2]_f^2\ 10^6$	Calc.	Obs.
0	100	0·512	13·1	6·7	6·7	70·15	29·85	2·89	1·69	4·9	17·8
20·7	79·3	0·767	5·66	4·3	3·4	91·25	8·75	7·73	1·18	9·1	24·4
					2·4	100	0	16·4	1·04	17·0	17·0
43·9	56·1	1·32	2·92	3·8	10·3						

The theory reproduces the minimum in the curve, but puts it at about 40% instead of about 22% of *iso*butyl vinyl ether. Beyond the minimum, the experimental results rise much more rapidly than those given by the theory. We attribute this to a failure of equation (2), which is based on the idea of two independent equilibria. It seems possible that the addition of 2-chloroethyl vinyl ether to the system *iso*butyl vinyl ether–iodine changes the equilibrium constant K_{t1} in the direction of a decrease, *i.e.*, making the *iso*butyl vinyl ether–iodine complex less stable. This may be a dielectric-constant effect as

we should expect the chloro-derivative to have a different dielectric constant from the other ethers. There is additional evidence for this theory in Fig. 1. Here we see that 56 mole % of 2-chloroethyl vinyl ether has suppressed the maximum velocity that was found for *iso*butyl vinyl ether at a monomer concentration of 0·8, which we take to mean that it has

FIG. 1. *The rate of copolymerisation as a function of total initial concentration of monomers. The arrow denotes the concentration at which the curve for pure* isobutyl *vinyl ether monomer reaches a maximum, but no maximum appears in the copolymerisation.*

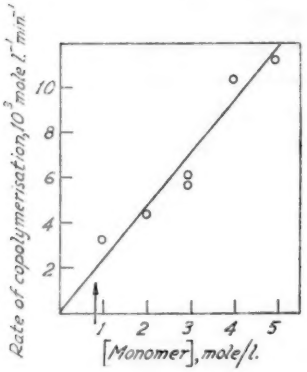
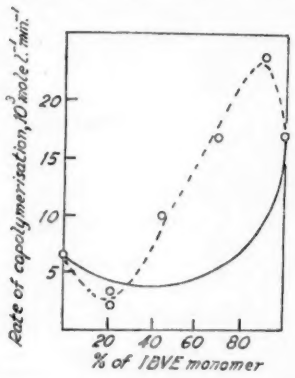


FIG. 2. *Rate of copolymerisation at varying ratios of* isobutyl *vinyl ether to 2-chloroethyl vinyl ether monomer. The broken line links the experimental points, while the full line is calculated from the theory.*



decreased the stability of the *iso*butyl vinyl ether–iodine complex. The existence of such maxima has been attributed in earlier papers of this series to the formation of stable vinyl ether–iodine complexes.

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THE UNIVERSITY, BRISTOL. [*Received, December 12th,* 1953.]

Analogues of Chloramphenicol. Part I.

By DOUGLAS S. MORRIS and SYLVIA D. SMITH.

[Reprint Order No. 4893.]

The nitro-group of chloramphenicol has been replaced by cyano-, carbamoyl, ethoxycarbonyl, and thiazolyl groups. The dichloroacetamido-group of chloramphenicol has been replaced by a ureido-group and attempts have been made to replace the nitro- by a ureido-group.

THIS paper describes variation of the chloramphenicol molecule, starting from DL-*threo*-2-acetamido-1-*p*-aminophenylpropane-1 : 3-diol (I; R = NH_2, R′ = Ac) which is prepared by catalytic hydrogenation of the readily available *p*-nitro-derivative. The amino-compound was converted by the Sandmeyer reaction into the cyano-compound, from which the ethoxycarbonyl derivative (I; R = CO_2Et, R′ = H) was prepared by the action of dry hydrogen chloride and ethanol, the acetyl group being removed. The free base, isolated as a gum, was acylated by treatment with methyl dichloroacetate. The carbamoyl compounds (I; R = NH_2·CO, R′ = Ac and $CHCl_2$·CO) were made by the action of alkaline hydrogen peroxide on the corresponding nitriles and the thiocarbamoyl compound by that of alcoholic ammoniacal hydrogen sulphide on (I; R = CN, R′ = Ac). This was used in

p-R·C_6H_4·CH(OH)·CH(NHR′)·CH_2·OH (I)

the preparation of the thiazoles (I; R = 4-methyl- and 4-*p*-nitrophenyl-2-thiazolyl, R′ = Ac or $CHCl_2$·CO) by reaction with the appropriate halogeno-ketone. The thiocarbamoyl derivative was not obtained when the *N*-dichloroacetyl-*p*-cyano-compound reacted with hydrogen sulphide in cold pyridine and triethylamine (cf. Fairful, Lowe, and Peak, *J.*, 1952, 742) or with alcoholic ammoniacal hydrogen sulphide. In the former reaction only triethylamine hydrochloride was obtained, along with oily decomposition products; this instability of the dichloroacetyl group in the presence of tertiary bases is in keeping with the observations of Van der Meer, Kofman, and Veldstra (*Rec. Trav. chim.*, 1953, **72**, 236).

The optically active ureido-compound (I; R = NO_2, R′ = CO·NH_2) from D-(−)-*threo*-2-amino-1-*p*-nitrophenyl-1 : 3-propanediol was prepared by means of potassium cyanate and hydrochloric acid. The racemic ureido-derivatives (I; R = CO·NH_2, R′ = Ac or CO·NH_2) were prepared in the same manner from the appropriate amines. The former was subjected to acid hydrolysis to effect deacetylation and gave intractable gums when attempts were made to prepare dichloroacetyl derivatives.

Antibacterial tests on the dichloroacetyl compounds described above showed activities less than 10% of that of chloramphenicol.

Experimental

DL-threo-2-*Acetamido*-1-p-*aminophenylpropane*-1 : 3-*diol*.—The corresponding nitro-compound (100 g.) in methanol (500 c.c.) was hydrogenated at room temperature and pressure in presence of 5% palladised strontium carbonate (1 g.). Absorption was rapid (*ca.* 1 l./min.) and the hot solution obtained owing to the exothermic reaction was filtered and cooled, to give the *amino*-compound as short needles (*ca.* 90%), m. p. 179—180° (Found: C, 59·0; H, 7·4; N, 12·5. $C_{11}H_{16}O_3N_2$ requires C, 58·9; H, 7·2; N, 12·5%).

DL-threo-2-*Acetamido*-1-p-*cyanophenylpropane*-1 : 3-*diol*.—The above amine (64 g.), dissolved in concentrated hydrochloric acid (80 c.c.), was diazotised with sodium nitrite (23 g.) in water (150 c.c.). The resulting solution was neutralised by sodium carbonate (15·3 g.) and added to a cold solution of sodium cyanide (51·6 g.) and nickel chloride (55·4 g.) in water (200 c.c.) which had been made alkaline with sodium carbonate (15·3 g.). The temperature was kept below 5° throughout. The solution was set aside overnight and filtered with "Hyflo Supercel," and the filtrate was extracted with hot ethyl acetate. From the extract the *nitrile* (42·9 g.) was obtained as pale yellow needles, m. p. 146—147° (Found: C, 61·2; H, 6·3; N, 11·9. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

DL-threo-2-*Dichloroacetamido*-1-p-*ethoxycarbonylphenylpropane*-1 : 3-*diol*.—The foregoing nitrile (10 g.) in ethanol (200 c.c.) was refluxed for 3½ hr. in a stream of dry hydrogen chloride. The alcohol was removed by distillation and the residue washed with ether, dissolved in water (30 c.c.), and heated on the steam-bath for 20 min. The solution was cooled and made alkaline with sodium hydroxide solution, to give an oil, which was extracted with ethyl acetate and dried, then recovered and heated in methanol (50 c.c.) on the steam-bath with methyl dichloroacetate for 1 hr. On working up in the usual manner the *ester* was obtained as needles [from ethyl acetate–light petroleum (b. p. 40—60°)] (3 g.), m. p. 109—110° (Found: C, 48·0; H, 5·1; N, 4·55; Cl, 21·6. $C_{14}H_{17}O_5NCl_2$ requires C, 48·0; H, 4·9; N, 4·0; Cl, 20·25%).

DL-threo-1-p-*Cyanophenyl*-2-*dichloroacetamidopropane*-1 : 3-*diol*.—The foregoing nitrile (5 g.) was deacetylated by dilute sulphuric acid (25 c.c.) on the steam-bath for 1 hr. The cooled solution was made alkaline and extracted with *n*-butanol, the base being isolated as a gum. This was refluxed in methanol with methyl dichloroacetate (4 c.c.) for 1 hr.; by working up in the usual manner the *dichloroacetyl* derivative (1 g.) was obtained as needles, m. p. 126—127° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 46·7; H, 4·1; N, 8·85; Cl, 21·7. $C_{12}H_{12}O_3N_2Cl_2$ requires C, 47·4; H, 4·0; N, 9·2; Cl, 23·4%).

DL-threo-2-*Acetamido*-1-p-*carbamylphenylpropane*-1 : 3-*diol*.—The cyano-compound (7·2 g.), obtained from the diazonium reaction above, was dissolved in ethanol (10 c.c.) and diluted with water (40 c.c.). 30% Hydrogen peroxide solution (6 c.c.) and 5N-sodium hydroxide (2 c.c.) were added. A vigorous reaction occurred and the temperature was kept at 20° by cooling. When the reaction had subsided, the temperature was raised to 40° for 10 min. The total reaction time was approx. 30 min. Extraction of the cold solution with *n*-butanol gave a pale brown resin which crystallised from *iso*propanol–ethyl acetate, to give the *amide* (3·6 g.), m. p. 157—158° after drying in a high vacuum (Found: C, 57·2; H, 6·7; N, 11·0. $C_{12}H_{16}O_4N_2$

requires C, 57·1; H, 6·4; N, 11·1%). The corresponding *dichloroacetamido*-compound, obtained analogously, had m. p. 137—138° [small needles from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 45·1; H, 4·6; N, 8·6; Cl, 21·0. $C_{12}H_{14}O_4N_2Cl_2$ requires C, 44·9; H, 4·4; N, 8·7; Cl, 22·1%).

DL-threo-2-*Acetamido*-1-p-*thiocarbamoylphenylpropane*-1 : 3-*diol*.—The corresponding cyano-compound (4·6 g.) in ethanol (25 c.c.) was added to a solution of ammonia in alcohol and a stream of hydrogen sulphide passed into the mixture until a green colour appeared. The solution was then heated in a pressure bottle at 70° for 1 hr.; after evaporation, the residue crystallised from boiling water, to give the *thioamide* as yellow prisms (3·5 g.), m. p. 211—212° (Found: C, 53·45; H, 6·0; N, 10·2; S, 11·9. $C_{12}H_{16}O_3N_2S$ requires C, 53·7; H, 6·0; N, 10·4; S, 12·0%). The 2-dichloroacetamido-derivative could not be obtained by this technique or by the passage of dry hydrogen sulphide for 2 hr. through a cold solution of the corresponding cyano-compound (1·6 g.) in dry pyridine (5 c.c.) and triethylamine (1·5 c.c.). Repeated washing with light petroleum and crystallisation of the residue from ethyl acetate gave triethylamine hydrochloride as needles, m. p. 251—252° (Found: C, 52·5; H, 11·7; N, 9·8; Cl, 24·1. Calc. for $C_6H_{16}NCl$: C, 52·3; H, 11·7; N, 10·2; Cl, 25·8%).

4-[p-(DL-threo-2-*Acetamido*-1 : 3-*dihydroxypropyl*)*phenyl*]-2-*methylthiazole*.—The corresponding thioamide (1·34 g.) was refluxed in ethanol (20 c.c.) and chloroacetone (0·4 c.c.) for 1 hr. The solvent was removed by distillation, the residue made alkaline with sodium hydrogen carbonate solution, and the product obtained as an oil by extraction with ethyl acetate. Crystallisation from ethyl acetate gave the *thiazole* (0·4 g.), m. p. 193—194° (Found: C, 58·1; H, 6·0; N, 9·0; S, 10·9. $C_{15}H_{18}O_3N_2S$ requires C, 58·8; H, 5·9; N, 9·15; S, 10·5%). The corresponding *dichloroacetamido*-derivative was obtained by heating the acetamido-derivative (1 g.) with 2N-sulphuric acid (10 c.c.) for 30 min. on the steam-bath and treating the free base, obtained by use of alkali and extraction with ethyl acetate, with methyl dichloroacetate in methanol for 15 min. on the steam-bath. The thiazole crystallised from methanol as needles, m. p. 204—205° (Found: C, 49·1; H, 4·5; N, 8·1; Cl, 20·0; S, 9·3. $C_{15}H_{16}O_3N_2SCl_2$ requires C, 48·0; H, 4·3; N, 7·5; Cl, 19·8; S, 8·55%).

4-[p-(DL-threo-2′-*Acetamido*-1′ : 3′-*dihydroxypropyl*)*phenyl*]-2-p-*nitrophenylthiazole*.—The thioamide (2·54 g.) was refluxed in ethanol (100 c.c.) with *p*-nitrophenacyl bromide (2·44 g.) for 3 hr. A yellow crystalline solid was formed which was isolated, washed with sodium hydrogen carbonate solution and water, and dried; it formed small prisms (2·3 g.), m. p. 236° (Found: C, 57·3; H, 4·7; N, 9·9; S, 8·3; $C_{20}H_{19}O_5N_3S$ requires C, 58·1; H, 4·6; N, 10·2; S, 7·75%). The corresponding *dichloroacetyl* derivative was obtained by isolation of the dry base and gradual extraction thereof (Soxhlet) into methanol and methyl dichloroacetate; it formed yellow needles, m. p. 234°, from methanol (Found: C, 49·9; H, 3·8; N, 8·5; Cl, 14·5; S, 6·4. $C_{20}H_{17}O_5N_3Cl_2S$ requires C, 49·8; H, 3·55; N, 8·7; Cl, 14·7; S, 6·6%).

D-threo-1-p-*Nitrophenyl*-2-*ureidopropane*-1 : 3-*diol*.—Chloramphenicol base (4·24 g.) was treated in the cold with 2N-hydrochloric acid (10 c.c.) and potassium cyanate (2 g.) in water (10 c.c.) and set aside overnight. The mixture was evaporated to dryness and the *ureido*-compound obtained by crystallisation from ethanol as needles, m. p. 170—171° (Found: C, 47·2; H, 5·5; N, 17·0. $C_{10}H_{13}O_5N_3$ requires C, 47·1; H, 5·1; N, 16·5%).

DL-threo-2-*Acetamido*-1-p-*ureidophenylpropane*-1 : 3-*diol*.—DL-*threo*-1-Acetamido-2-*p*-aminophenylpropane-1 : 3-diol (4·48 g.) was treated as in the preceding preparation, and the *ureido*-compound crystallised from water as needles, m. p. 218° (decomp.) (Found: C, 54·3; H, 6·7; N, 15·4. $C_{12}H_{17}O_4N_3$ requires C, 53·9; H, 6·4; N, 15·7%).

DL-threo-2-*Ureido*-1-p-*ureidophenylpropane*-1 : 3-*diol*.—DL-*threo*-2-Amino-1-*p*-aminophenylpropane-1 : 3-diol (3·64 g.) was treated as in the preceding preparation with 2N-hydrochloric acid (20 c.c.) and potassium cyanate (4 g.). The *diureido*-derivative was obtained from aqueous ethanol as a white microcrystalline solid, m. p. 199° (decomp.) (Found: C, 48·3; H, 6·2; N, 21·4. $C_{11}H_{16}O_4N_4$ requires C, 49·3; H, 6·0; N, 20·9%).

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*Analogues of Chloramphenicol. Part II.**

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The *p*-hydroxy-analogue of chloramphenicol has been prepared from *p*-benzyloxyacetophenone, and an abnormal Meerwein reduction product has been investigated. The analogue obtained gives a known methyl ether having the *threo*-configuration. A 3 : 5-di-iodo-derivative has been prepared.

Attempts made to replace the nitro-group of chloramphenicol by hydroxyl, by means of reduction and diazotisation were unsuccessful, and recourse was taken to an adaptation of Long and Troutman's general method (*J. Amer. Chem. Soc.*, 1949, **71**, 2437), starting from *p*-hydroxyacetophenone. This ketone was not obtained by us in the yields claimed by Irvine and Robinson for their method (*J.*, 1927, 2091) or adaptations of this and earlier methods. It was readily and consistently prepared, however, by Fries rearrangement of phenyl acetate (B.I.O.S. Final Report 766, p. 93). *p*-Benzoyloxyacetophenone was prepared by the usual Schotten–Baumann technique and was converted into α-acetamido-*p*-benzoyloxyacetophenone without isolation of the intermediate products in pure states (cf. Corrigan, Longeman, and Moore, *J. Amer. Chem. Soc.*, 1945, **67**, 1894). The acetamido-ketone (I; R = Bz) was prepared by the standard hydroxymethylation technique (Long and Troutman, *loc. cit.*) and reduced by the Meerwein–Pondorff method or by catalytic hydrogenation to (II; R = Bz). Owing to transesterification in the Meerwein–Pondorff reduction, the yields were low and repeated crystallisation was essential. The hydrogenation product which differed in m. p. from the Meerwein reduction product was more readily purified.

p-RO·C$_6$H$_4$·CO·CH(NHAc)·CH$_2$·OH (I)

p-RO·C$_6$H$_4$·CH(OH)·CH(NHAc)·CH$_2$·OH (II)

Hydrolysis of (II; R = Bz) by dilute hydrochloric acid gave a 2-amino-*p*-benzoyloxy-compound, m. p. 145—146°; an isomeric base, m. p. 184°, was similarly obtained on use of dilute sulphuric acid. Low yields of these compounds, however, precluded further investigation.

Attention was then turned to *p*-benzyloxyacetophenone and satisfactory techniques were devised for the preparation of (II; R = Ph·CH$_2$). The reduction was carried out by the Meerwein–Pondorff method or by sodium borohydride, but hydrogenation in presence of Raney nickel caused debenzylation as the primary reaction and complete reduction afforded an intractable gum. The Meerwein–Pondorff reduction product was hydrolysed with dilute sulphuric acid to give a crystalline sulphate from which the free 2-amino-*p*-benzyloxy-compound was readily obtained in a pure condition. Catalytic hydrogenation in ethanol in the presence of palladised strontium carbonate then gave the phenolic amine which with or without isolation was converted into the required analogue of chloramphenicol by the action of methyl dichloroacetate.

The 3 : 5-di-iodo-derivative was prepared by the action of aqueous sodium iodide and iodine solution in presence of sodium hydrogen carbonate. Methylation of (II; R = H) gave a methyl ether melting 5° higher than stated by Buu-Hoï (*J.*, 1951, 255) and 14° lower than stated by Rebstock and Pfeiffer (*J. Amer. Chem. Soc.*, 1952, **74**, 3207). Consequently (II; R = Ph·CH$_2$) is regarded as having a *threo*-configuration.

During one Meerwein–Pondorff reduction of (I; R = Ph·CH$_2$) there was obtained a compound $C_{18}H_{17}O_3N$, which corresponds to the loss of one molecule of water from the starting material. The ultra-violet spectrum of this compound had an intense maximum

(III) Ph·CH$_2$·O·C$_6$H$_4$·CO·CH(NHAc)·CH$_2$·OAc ⟶ Ph·CH$_2$·O·C$_6$H$_4$·CO·C(NHAc):CH$_2$ (IV)

at 285 mμ, indicative of a phenyl ketone, and this taken in conjunction with its mode of formation and the uptake of three mols. of hydrogen on catalytic hydrogenation is most readily accommodated by structure (IV). This was confirmed by treatment of the di-

* Part I, preceding paper.

acetate (III) with boiling quinoline, elimination of acetic acid occurring to give the Meerwein–Pondorff reduction product in high yield. The formation of compounds of type (IV) from β-hydroxypropiophenones by the action of acetic anhydride and pyridine has been observed by Huebner, Diassi, and Scholz (*J. Org. Chem.*, 1953, **18**, 21); no such products have previously been recorded as arising during Meerwein–Pondorff reduction.

Experimental

p-*Hydroxyacetophenone*.—Phenyl acetate (1 kg.) was heated, with stirring, in a 4-l. beaker. Finely ground aluminium chloride (1·1 kg.) was added portionwise, the temperature being kept at 90—95°. Benzene was added to control frothing and the reaction was complete in 2—3 hr., giving a clear melt. Decomposition was effected with ice and concentrated hydrochloric acid as usual. The product was distilled with steam to remove the *ortho*-isomeride. The distillate and residue were worked up separately to give *p*- (370 g.), m. p. 108°, and *o*-hydroxyacetophenone (258 g.), b. p. 98°/6 mm. The former was purified by crystallisation from boiling water or by vacuum-distillation.

α-*Acetamido*-p-*benzoyloxyacetophenone*.—The hexamine salt (95 g.) of *p*-benzoyloxy-ω-iodoacetophenone (prepared by Corrigan's method, *J. Amer. Chem. Soc.*, 1945, **67**, 1894) was hydrolysed by stirring it with ethanol (500 c.c.) and concentrated hydrochloric acid (250 c.c.) for 16 hr. The crude amino-ketone hydrochloride obtained by filtration was stirred for 30 min. with an excess of sodium acetate solution and acetic anhydride in ice-water. The *acetamidoketone* was obtained as needles (22 g.), m. p. 167—168°, from ethyl acetate (Found: C, 68·9; H, 5·0; N, 4·8. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1; N, 4·7%).

2-*Acetamido*-1-p-*benzoyloxyphenylethanol*.—The foregoing acetamido-ketone (2·97 g.) was hydrogenated in ethanol in presence of Raney nickel, to yield the *alcohol* as needles, m. p. 146—148° (from ethyl acetate) (Found: C, 68·1; H, 5·7; N, 5·2. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7; N, 4·7%).

α-*Acetamido*-p-*benzoyloxy*-β-*hydroxypropiophenone*.—The above acetamido-ketone (15 g.) in ethanol (100 c.c.) was stirred with aqueous formaldehyde (10 c.c.; 38%) and sodium hydrogen carbonate (1·0 g.) at 40—45° for 1 hr. The solution was treated with charcoal, filtered, and partly evaporated. On cooling, the *hydroxy-ketone* was obtained as plates (10 g.) (from ethyl acetate), m. p. 168° (Found: C, 66·6; H, 5·4; N, 4·4. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2; N, 4·3%).

Reductions of α-*Acetamido*-p-*benzoyloxy*-β-*hydroxypropiophenone*.—(a) *Meerwein–Pondorff reduction*. The preceding ketone (5 g.) was slowly distilled with a solution of aluminium *iso*propoxide (5 g.) in dry *iso*propanol (50 c.c.). When no acetone was present in the distillate, the residue was decomposed by boiling with water for 10 min. and filtered. Evaporation of the filtrate gave a residue which readily crystallised from ethyl acetate, to give a crude *aminodiol* (3·3 g.), m. p. 138° (Found: C, 65·65; H, 5·6; N, 4·6. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8; N, 4·3%). Further crystallisations from ethyl acetate raised the m. p. to 147—148° (Found: C, 65·1; H, 5·9; N, 4·5%). Repeated crystallisations gradually raised the m. p. to 162° (Found: C, 65·1; H, 5·65%).

(b) *Catalytic hydrogenation*. The preceding propiophenone (12·3 g.) was hydrogenated in ethanol in presence of Raney nickel. Repeated crystallisation from ethyl acetate gave an *acetamido-diol* (5·6 g.), m. p. 177° (the mother liquors on evaporation gave only intractable gums) (Found: C, 65·5; H, 5·55; N, 4·35%).

Acid Hydrolysis of 2-*Acetamido*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol obtained by Hydrogenation*.—(*a*) Hot concentrated hydrochloric acid caused extensive decomposition. (*b*) The acetamido-diol (1·7 g.), 2N-hydrochloric acid (12·7 ml.), and ethanol (10 ml.) was heated for 90 min. on the steam-bath. The mixture was cooled, diluted with water (50 ml.), and made alkaline with sodium hydroxide solution. 2-*Amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol* (0·94 g.), m. p. 134—135°, was obtained and crystallised first from aqueous ethanol to m. p. 141—142° and finally from ethanol and ethyl acetate as plates, m. p. 145—146° (Found: C, 66·7; H, 5·9; N, 4·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%). (*c*) The acetamido-diol (4·85 g.) was refluxed for 2 hr. with 2N-sulphuric acid (5 c.c.). On cooling, a crystalline compound, m. p. 225°, was obtained. When washed with hot ethanol and recrystallised from water, 2-*amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol sulphate* was obtained as plates, m. p. 246° (Found: C, 53·7; H, 5·65; N, 4·5; S, 4·8. $C_{16}H_{17}O_4N,\frac{1}{2}H_2SO_4,H_2O$ requires C, 5·42; H, 5·65; N, 4·0; S, 4·55%).

Another *form* of 2-*amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol* was obtained by treatment of the sulphate with sodium hydrogen carbonate solution. When crystallised from methanol and ethyl acetate needles were obtained, having m. p. 184° (Found : C, 67·1; H, 5·5; N, 4·6%).

p-*Benzyloxyacetophenone*.—Prepared according to Priestly and Moness (*J. Org. Chem.*, 1940, **5**, 355) in almost quantitative yield, this had m. p. 93°.

ω-*Acetamido*-p-*benzyloxyacetophenone*.—The foregoing ketone (113 g.) in chloroform (200 c.c.) and sodium-dried ether (500 c.c.) was treated dropwise with bromine (25·8 c.c.) at 10°. Bromination of slightly impure ketone was more rapid than that of pure ketone; bromination in presence of suspended calcium carbonate was extremely slow. It was necessary in some cases to warm the solution at the start of bromination and to expose the solution to ultra-violet light. Once the reaction was initiated, bromination was very rapid and cooling was essential. The solution obtained was added with stirring to hexamethylenetetramine (200 g.) in chloroform (1500 c.c.), and stirring continued for 2 hr. The damp white precipitate of hexamethylene addition product obtained by filtration was hydrolysed by stirring with ethanol (1 l.) and concentrated hydrochloric acid (500 c.c.) overnight. The crude α-amino-ketone hydrochloride obtained by filtration was acetylated in presence of ice and ice-water (1 l.) with sodium acetate (164 g.) and acetic anhydride (103 c.c.) by stirring for 2 hr. ω-*Acetamido*-p-*benzyloxyacetophenone* was obtained by crystallisation of the product from methanol as needles (75 g.), m. p. 138° (Found : C, 71·55; H, 5·8; N, 5·05. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·05; N, 4·9%); $\lambda_{max.}$ 281 mμ (ε 16,130).

ω-*Acetamido*-p-*hydroxyacetophenone*.—The foregoing benzyl ether was hydrogenolysed in the presence of palladised strontium carbonate, to give the *phenol* as prisms, m. p. 179—180° (from ethyl acetate) (Found : C, 62·2; H, 5·7; N, 8·65. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·25%), $\lambda_{max.}$ 285 mμ (ε 15,350).

α-*Acetamido*-p-*benzyloxy*-β-*hydroxypropiophenone*.—The foregoing ketone (75 g.) was stirred at 45° for 1½ hr. with aqueous formaldehyde (50 c.c.; 38%) and sodium hydrogen carbonate (5 g.). The hot solution was treated with charcoal, filtered, and on cooling yielded the *ketone* (62 g.) as plates, m. p. 147—148° (Found : C, 68·8; H, 6·0; N, 5·3. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%).

α-*Acetamido*-p-*hydroxy*-β-*hydroxypropiophenone*.—The foregoing benzyl ether was hydrogenolysed in alcohol in the presence of Raney nickel or palladised strontium carbonate, to give the *ketone* as needles (from ethyl acetate), m. p. 178—179° (Found : C, 59·4; H, 6·0; N, 5·75. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%).

DL-threo-2-*Acetamido*-1-p-*benzyloxyphenylpropane*-1 : 3-*diol*.—(*a*) A mixture of dry *iso*propanol (100 c.c.), aluminium *iso*propoxide (3 g.), and α-acetamido-*p*-benzyloxy-β-hydroxypropiophenone (3 g.) was slowly distilled for 1½ hr. until no acetone was detectable in the distillate. The residue was heated on the steam-bath for 10 min. with the addition of water (10 c.c.), then filtered, and the solid was extracted with hot methanol. The combined extracts, on evaporation and repeated crystallisation from ethyl acetate, gave the *diol* as short needles, m. p. 169—170° (Found : C, 69·0; H, 7·0; N, 4·6. $C_{18}H_{21}O_4N$ requires C, 68·55; H, 6·7; N, 4·4%).

In one such experiment another *compound* was obtained as needles, m. p. 137—138° (Found : C, 73·1; H, 5·9; N, 4·8. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%), $\lambda_{max.}$ 222 and 285 mμ (ε 19,220, 14,510).

(*b*) The propiophenone (3·13 g.) in ethanol (80 c.c.) was stirred at room temperature for 10 min. with a solution of sodium borohydride (0·2 g.) in ethanol (20 c.c.). The mixture was diluted with water (20 c.c.), acidified with glacial acetic acid, and evaporated to dryness. The product was repeatedly crystallised from ethyl acetate and was identical with the diol obtained as in (*a*).

DL-threo-2-*Acetamido*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—Debenzylation of the foregoing diol in alcohol was carried out in the presence of palladised strontium carbonate. The *phenol* was obtained as needles, m. p. 175° (decomp.), by crystallisation from ethyl acetate or dioxan (Found : C, 57·9; H, 6·5; N, 5·6. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7; N, 6·2%). The phenol (1 g.) was methylated by refluxing ethyl methyl ketone (150 c.c.), absolute alcohol (50 c.c.), anhydrous potassium carbonate (2 g.), and methyl iodide (5 c.c.) for 6 hr. The methyl ether, m. p. 128°, was obtained on crystallisation from water (Found : C, 59·55; H, 7·2; N, 6·0. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·2; N, 5·85%).

DL-threo-2-*Acetamido*-1-(4-*hydroxy*-3 : 5-*di*-*iodophenyl*)*propane*-1 : 3-*diol*.—The foregoing acetamido-compound (0·14 g.) in saturated sodium hydrogen carbonate solution (10 c.c.) was

treated dropwise with an aqueous solution (1·3 c.c. of 1·9N) of iodine and sodium iodide. After 30 min. the solution was filtered and acidified with dilute sulphuric acid. The precipitated solid was crystallised from aqueous ethanol to give the *di-iodo*-compound, m. p. 186° (decomp.) (Found: C, 28·3; H, 2·8; N, 2·8; I, 52·5. $C_{11}H_{13}O_4NI_2$ requires C, 27·7; H, 2·75; N, 2·9; I, 52·8%).

DL-threo-2-*Amino*-1-p-*benzoyloxypropane*-1 : 3-*diol*.—The acetyl derivative (1·5 g.) was heated under reflux for 30 min. with N-sulphuric acid (25 c.c.). On cooling, a *sulphate* (1·25 g.), m. p. 229—230° (decomp.), was obtained as plates (Found: C, 56·65; H, 6·55; N, 4·8; S, 5·4. $C_{16}H_{19}O_3N,\frac{1}{2}H_2SO_4,H_2O$ requires C, 56·5; H, 6·5; N, 4·1; S, 4·7%). When this was made alkaline with hot sodium hydrogen carbonate solution, the free *base* (0·6 g.) was obtained, forming plates, m. p. 126—127°, from water (Found: C, 69·6; H, 6·9; N, 4·95. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%).

DL-threo-2-*Amino*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—The foregoing base (1·6 g.) was debenzylated by hydrogenation in alcohol in presence of palladised strontium carbonate, to give a gum which was dissolved in methanol and ethyl acetate and set aside in the refrigerator for one week. The *phenolic base* was obtained as needles (0·6 g.), m. p. 138° (Found: C, 58·1; H, 6·6; N, 7·7. $C_9H_{13}O_3N$ requires C, 59·0; H, 7·15; N, 7·65%).

DL-threo-2-*Dichloroacetamido*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—The phenolic base (0·1 g.) obtained as in the preceding paragraph was refluxed with methyl dichloroacetate (2 c.c.) and methanol (5 c.c.) for 20 min. Evaporation and repeated trituration with light petroleum gave an oil, which was taken up in cold water and extracted twice with ethyl acetate. From the ethyl acetate extract the *dichloroacetamide* was obtained as needles, m. p. 122—124°, by evaporation and treatment of the residue with light petroleum (Found: C, 45·3; H, 4·7; N, 4·3; Cl, 22·1. $C_{11}H_{13}O_4NCl_2$ requires C, 44·9; H, 4·8; N, 4·8; Cl, 24·1%).

DL-threo-2-*Dichloroacetamido*-1-(4-*hydroxy*-3 : 5-*di-iodophenyl*)*propane*-1 : 3-*diol*.—The foregoing dichloroacetamido-compound was iodinated in the same manner as the acetamido-compound; the *product* crystallised from aqueous alcohol as a monohydrate, m. p. 165° (decomp.), a pale buff microcrystalline powder (Found: N, 2·5; Halogen, 57·6. $C_{11}H_{11}O_4NCl_2I_2,H_2O$ requires N, 2·5; Halogen, 57·6%).

α-*Acetamido*-β-*acetoxy*-p-*benzyloxypropiophenone*.—α-Acetamido-*p*-benzyloxy-β-hydroxypropiophenone (1 g.) in dry pyridine (6 c.c.) and acetic anhydride (0·4 c.c.) was left for 48 hr. The mixture was diluted with water, and the *diacetyl* derivative crystallised from ethanol as needles, m. p. 132° (Found: C, 66·5; H, 5·9; N, 4·1. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2; N, 4·1%), $\lambda_{max.}$ 282 mμ (ε 16,200).

α-*Acetamido*-p-*benzyloxyacrylophenone*.—The foregoing diacetate (0·4 g.) and quinoline (3 c.c.) were boiled for 3 min. and then poured into water. Crystallisation from methanol afforded the ketone as needles, m. p. 138°, alone or on admixture with the abnormal Meerwein–Pondorff reduction product described above.

This ketone (1·0 g.) absorbed 3 mols. of hydrogen in ethanol in presence of palladised strontium carbonate, giving 2-*acetamido*-1-p-*hydroxyphenylpropan*-1-*ol*, prisms, m. p. 194—195° (from water) (Found: C, 63·0; H, 7·3; N, 6·5. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

The authors are indebted to Dr. R. E. Bowman for many helpful discussions and to Miss E. M. Tanner for the measurement of spectra.

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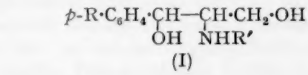
*Analogues of Chloramphenicol. Part III.**

By David D. Evans, Douglas S. Morris, Sylvia D. Smith, and David J. Tivey.

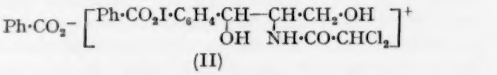
[Reprint Order No. 4895.]

The nitro-group of chloramphenicol has been replaced by trimethylammonium, iodoxyl, iodoso-, and benzyl groups. The *threo*-configuration of the known iodo-analogue of chloramphenicol has been confirmed.

The nitro-group of chloramphenicol has been replaced by strongly *meta*-directing groups, namely, trimethylammonium and iodoxyl, in the expectation that antibacterial activity might be retained. D-(−)-*threo*-2-Acetamido-1-*p*-nitrophenylpropane-1 : 3-diol was catalytically hydrogenated to the corresponding *p*-amino-compound (I; R = NH_2, R′ = Ac). Hydrogenation was continued in the presence of formaldehyde, to give the dimethylamino-compound, which was converted by standard methods into the hydrochloride of the quaternary chloride (I; R = NMe_3}Cl, R′ = H). The base (I; R = NMe_3}Cl, R′ = H) itself, obtained from the hydrochloride by treatment with the predetermined amount of alkali, was not obtained crystalline and was converted into the analogue of chloramphenicol (I; R = NMe_3}Cl, R′ = $CHCl_2$·CO) by means of methyl dichloroacetate.



(I)



(II)

The dimethylamino-compound (I; R = NMe_2, R′ = H) was prepared from the acetamido-compound by hydrolysis with dilute sulphuric acid (more efficacious than hydrochloric acid or sodium hydroxide), but attempts to convert it into a dichloroacetyl derivative gave tars (cf. attempts by Van der Meer, Kofman, and Veldstra, *Rec. Trav. chim.*, 1953, **72**, 286, to prepare a pyridyl analogue).

The iodo-analogue (I; R = I, R′ = $CHCl_2$·CO), prepared by Bambas, Troutman, and Long (*J. Amer. Chem. Soc.*, 1950, **72**, 4445) and regarded in virtue of its mode of preparation as having a *threo*-configuration, has been catalytically dehalogenated to (±)-*threo*-2-acetamido-1-phenylpropane-1 : 3-diol (Controulis, Rebstock, and Crooks, *J. Amer. Chem. Soc.*, 1949, **71**, 2463; Fodor, Kiss, and Sallay, *J.*, 1951, 1858). The iodo-analogue now of proven *threo*-configuration has been converted into the iodoxyl (I; R = IO_2, R′ = $CHCl_2$·CO) and the dibenzoyliodoso-analogue (II) by the action of perbenzoic acid.

The *p*-benzyl analogue (I; R = Ph·CH_2, R′ = $CHCl_2$·CO) has been prepared in both *threo*- and *erythro*-forms by the general method of Long and Troutman (*J. Amer. Chem. Soc.*, 1949, **71**, 2473).

The identity of *p*-benzylphenacyl bromide was established by the preparation of a pyridinium bromide and conversion of the latter into *p*-benzylbenzoic acid, thereby indicating that during bromination of *p*-benzylacetophenone no attack occurred on the bridge methylene group. Acetamido-*p*-benzylacetophenone reacted readily with formaldehyde, one or two hydroxymethyl groups being readily introduced. 2-Acetamido-1-*p*-benzylphenylpropane-1 : 3-diol was readily obtained in both the *threo*- and the *erythro*-form by catalytic reduction or Meerwein–Pondorff reduction of the corresponding ketone. The diol obtained in preponderance by the Meerwein reduction was regarded by analogy with other reductions in this field as having the *threo*-configuration.

Antibacterial tests on the dichloroacetyl compounds described above will be reported elsewhere.

Experimental

Acetylation of D-(−)-threo-2-*Amino*-1-p-*nitrophenylpropane*-1 : 3-*diol*.—Acetic anhydride (46 c.c.) was added to a thick slurry of D-(−)-*threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (75 g.), sodium acetate (45 g.), and crushed ice. The mixture was vigorously shaken for 60 min.,

* Part II, preceding paper.

then extracted thoroughly with ethyl acetate, and the ethyl acetate extracts were washed to neutrality, dried, and evaporated. The residue was crystallised twice from ethyl acetate, to give the *N*-acetyl derivative (61 g.), m. p. 125—127°, in agreement with Rebstock, Crooks, Controulis, and Bartz (*J. Amer. Chem. Soc.*, 1949, **71**, 2458).

D-(−)-threo-2-*Acetamido*-1-p-*dimethylaminophenylpropane*-1 : 3-*diol*.—The foregoing acetyl derivative (71 g.) was hydrogenated in ethanol (250 c.c.) in presence of palladised charcoal (3·2 g.; 10% of PdO). After hydrogenation equivalent to the reduction of the nitro-group, aqueous formaldehyde (65 c.c. of 40%) was added and hydrogenation continued to completion. The residue (64 g.) obtained by removal of the catalyst and solvent crystallised from ethyl acetate, giving the *dimethylamino*-compound (44 g.) as plates, m. p. 136—139·5°, $[\alpha]_D^{20}$ −20·1° (*c* 1·05 in 96% ethanol) (Found: C, 61·5; H, 8·15; N, 11·2. $C_{13}H_{20}O_3N_2$ requires C, 61·9; H, 8·0; N, 11·1%).

The racemic *compound*, obtained similarly, formed pale yellow crystals, m. p. 159·5—160·5°, from methanol (Found: C, 61·4; H, 7·9; N, 11·3%).

p-[D(−)-threo-2-*Amino*-1 : 3-*dihydroxypropyl*]*phenyltrimethylammonium Derivatives*.—The solution of the dimethylamino-compound in ethanol obtained, after removal of the catalyst as in the preceding hydrogenation, from D-(−)-*threo*-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol (30 g.) was made up to 600 c.c. A portion (100 c.c.) of this solution was evaporated to dryness and the residue set aside for 2 days with a mixture of chloroform (20 c.c.), ethanol (2 c.c.), and methyl sulphate (10 c.c.). Treatment with acetone gave an insoluble red oil, which was dissolved in water (15 c.c.), treated with barium chloride (5 g.) and concentrated hydrochloric acid (15 c.c.), and warmed on the steam-bath for 45 min. Barium sulphate was filtered off, the filtrate evaporated to dryness *in vacuo*, and the residue thrice extracted with hot absolute alcohol. The *chloride hydrochloride* precipitated by acetone crystallised from hot ethanol as hygroscopic needles, m. p. 237° (after drying *in vacuo*), $[\alpha]_D^{20}$ −28·7° (*c* 1·16 in 96% ethanol) (Found: N, 9·4; Cl, 23·7. $C_{12}H_{22}O_2N_2Cl_2$ requires N, 9·4; Cl, 23·9%).

This salt (2·97 g.) in water (4 c.c.) was neutralised with N-sodium hydroxide (10 c.c.). The residue obtained by evaporation *in vacuo* was extracted with absolute alcohol to yield a pale yellow gum. The latter was refluxed in methanol (5 c.c.) with methyl dichloroacetate (5 c.c.) for 3 hr. and finally evaporated to dryness to give a hygroscopic gum. Treatment in ethanol with charcoal and evaporation gave a deliquescent foam, and crystallisation thereof from absolute alcohol gave small needles, m. p. 115—120°, $[\alpha]_D^{20}$ +21·7° (*c* 1·07 in H_2O), of the N-*dichloroacetamide chloride* (Found: N, 7·5; total Cl, 27·8; Cl^-, 9·3. $C_{14}H_{21}O_3N_2Cl_3$ requires N, 7·5; total Cl, 28·6; Cl^-, 9·6%).

D-(−)-threo-2-*Amino*-1-p-*dimethylaminophenylpropane*-1 : 3-*diol*.—The acetyl derivative (17 g.) was refluxed with 2N-sulphuric acid (100 c.c.) for 2 hr. and distilled with steam. After treatment with charcoal, the solution was treated with an excess of barium carbonate, filtered hot, and evaporated with the ethanolic washings to dryness *in vacuo*. The *base* crystallised from chloroform or *iso*propanol and after high-vacuum sublimation was a white solid, m. p. 143—145°, $[\alpha]_D^{20}$ −24·5° (*c* 0·54 in 96% ethanol) (Found: C, 62·6; H, 8·5; N, 13·1. $C_{11}H_{18}O_2N_2$ requires C, 62·8; H, 8·6; N, 13·3%).

p-(DL-threo-2-*Acetamido*-1 : 3-*dihydroxypropyl*)*phenyltrimethylammonium Chloride Hydrochloride*.—The racemic dimethylamino-compound (4·0 g.), methanol (11·5 c.c.), and methyl iodide (20 c.c.) were heated on the steam-bath for 15 min. and evaporated to dryness *in vacuo*, to give a solid foam. This (3·7 g.) with the addition of 18% hydrochloric acid (20 c.c.) was evaporated on the steam-bath to a gum. After several weeks, the gum gave the crystalline *chloride hydrochloride*, m. p. 165—167°, on trituration with ethanol, and was finally purified by recrystallisation from ethanol–acetone as short needles, m. p. 235—237° (Found: C, 48·5; H, 7·5; N, 9·4. $C_{12}H_{22}O_2N_2Cl_2$ requires C, 48·3; H, 7·15; N, 10·4%).

Hydrogenation of the Iodo-analogue of Chloramphenicol to DL-threo-2-*Acetamido*-1-*phenylpropane*-1 : 3-*diol*.—The iodo-analogue (2·02 g.) was hydrogenated in ethanol (100 c.c.) containing 5N-sodium hydroxide (4 c.c.) and 5% palladised strontium carbonate (0·5 g.). The residue obtained by removal of the catalyst and solvent was dissolved in water and shaken with a few drops acetic anhydride and sodium acetate solution. Extraction of the aqueous mixture with ethyl acetate gave a residue which crystallised from ethyl acetate as needles, m. p. 132—133°, undepressed by admixture with authentic (±)-*threo*-2-acetamido-1-phenylpropane-1 : 3-diol.

DL-threo-2-*Dichloroacetamido*-1-p-*iodoxyphenylpropane*-1 : 3-*diol*.—The iodo-analogue (2 g.), dissolved in dimethylformamide (2 c.c.), was treated with a chloroformic solution of perbenzoic acid (132 c.c. containing 0·0378 g./c.c.) and set aside for 48 hr. The *iodoxyl* compound (1·1 g.)

was obtained as a white crystalline solid, m. p. 105° (decomp.) (Found : C, 29·5; H, 3·1; N, 2·9; Halogen, 43·2%; equiv., 106. $C_{11}H_{12}O_5NCl_2I$ requires C, 30·2; H, 2·8; N, 3·2; Halogen, 45·4%; equiv., 109).

DL-threo-1-p-*Dibenzoyliodosophenyl*-2-*dichloroacetamidopropane*-1 : 3-*diol*.—The iodo-analogue (4·5 g.) in dimethylformamide (2 c.c.) was treated with a chloroformic solution of perbenzoic acid (250 c.c. containing 0·00876 g./c.c.) and set aside in the refrigerator for 16 hr. The *iodoso*-derivative was obtained as plates, m. p. 156—157° (Found : C, 45·8; H, 3·5; N, 2·3%; equiv., 318. $C_{25}H_{22}O_7NICl_2$ requires C, 46·5; H, 3·4; N, 2·2%; equiv., 323).

p-*Benzylacetophenone*.—Acetyl chloride (360 c.c.) was slowly added to a stirred solution of diphenylmethane (1 kg.) in carbon disulphide (730 c.c.) and finely ground aluminium chloride (610 g.), at <0°. Stirring was continued for 2 hr. during which room temperature was attained. The solution was poured on crushed ice and concentrated hydrochloric acid, the carbon disulphide layer was washed to neutrality, dried, and evaporated, and the residue was distilled to give *p*-benzylacetophenone, b. p. 188—190°/5 mm. (needles), m. p. 39° [from light petroleum (b. p. 40—60°)] (cf. Duval, *Compt. rend.*, 1908, **146**, 341).

p-*Benzylphenacyl Bromide*.—*p*-Benzylacetophenone (21 g.), in chloroform (100 c.c.), was treated at −10° to 0° dropwise with bromine (17 g.). The solution was washed to neutrality with sodium carbonate solution and water, dried (Na_2SO_4), and evaporated to an oil (29·2 g.) which from light petroleum (b. p. 40—60°) and then methanol gave the *phenacyl bromide* as needles, m. p. 47·5—49·5° (Found : Br, 26·3. $C_{15}H_{13}OBr$ requires Br, 27·6%).

p-*Benzylphenacylpyridinium Bromide*.—*p*-Benzylphenacyl bromide (14·5 g.) and dry pyridine (5·0 c.c.) were mixed and warmed for 5 min. on the steam-bath. The pyridinium bromide formed hygroscopic needles, m. p. 72—83°, from ethanol (Found : C, 62·8; H, 5·1; N, 3·8; Br, 20·25. $C_{20}H_{18}ONBr,H_2O$ requires C, 62·2; H, 5·2; N, 3·6; Br, 20·7%). When it (3·68 g.) was warmed for 12 min. on the steam-bath with 10% sodium hydroxide solution (14 c.c.), methanol (84 c.c.), and water (280 c.c.) it yielded, on acidification, *p*-benzylbenzoic acid, m. p. 156—157°.

p-*Benzylphenacylamine Hydrochloride*.—*p*-Benzylphenacyl bromide (11 g.) in chlorobenzene (20 c.c.) was treated with hexamethylenetetramine (6 g.) in dry chlorobenzene (100 c.c.) at 40° and set aside overnight. The quaternary *salt* crystallised from acetone as needles, m. p. 95—105° (Found : N, 13·6; Br, 19·0. $C_{21}H_{25}ON_4Br$ requires N, 13·1; Br, 18·6%). It could not be prepared in chloroform.

The salt (12·9 g.) was warmed to 40° with ethanol (30 c.c.) and concentrated hydrochloric acid (15 c.c.), then set aside overnight. The *amino-ketone hydrochloride* was purified by crystallisation first from water and, finally, from dilute hydrochloric acid, to give plates, m. p. 194—195° (Found : C, 69·0; H, 6·5; Cl, 13·3. $C_{15}H_{16}ONCl$ requires C, 68·8; H, 6·2; Cl, 13·5%).

The hydrochloride (5·3 g.) was shaken with sodium acetate (4·1 g.), acetic anhydride (3 c.c.), and ice-water (40 c.c.) for 3 hr. The *acetamido-ketone*, m. p. 113·5—114·5°, was obtained as plates from acetone (Found : C, 76·2; H, 6·3; N, 5·3. $C_{17}H_{17}ON$ requires C, 76·3; H, 6·4; N, 5·2%). It was also prepared in *ca.* 25% yield without isolation of the intermediate.

α-*Acetamido*-p-*benzyl*-β-*hydroxypropiophenone*.—The pH of a mixture of 40% aqueous formaldehyde (2 c.c.), the acetamido-ketone (5·3 g.), and ethanol (15 c.c.) was adjusted to 9·0 by 2N-sodium hydroxide; after 3 min. a clear solution was obtained, and after a further 5 min. the mixture was diluted with water (27 c.c.). An oil was precipitated, extracted with ethyl acetate, washed to neturality, dried, and recovered by evaporation. The β-*hydroxypropiophenone* formed needles (80%), m. p. 118°, from ethyl acetate (Found : C, 72·6; H, 6·5; N, 5·0. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). It was found that the usual time (1—3 hr.) for this reaction resulted in the formation of α-*acetamido*-p-*benzyl*-β-*hydroxy*-α-*hydroxymethyl*-*propiophenone* in good yield as needles, m. p. 161—163°, from ethyl acetate (Found : C, 69·4; H, 6·2; N, 4·3. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5; N, 4·3%).

threo- *and* erythro-2-*Acetamido*-1-p-*benzylphenylpropane*-1 : 3-*diol*.—(*a*) The β-hydroxypropiophenone (3·5 g.) was distilled with *iso*propanol (200 c.c.) and aluminium *iso*propoxide (4 g.) until no further acetone was detected in the distillate. On working up in the usual manner, two *propanediols* were obtained by crystallisation from ethyl acetate. The first (2·0 g.) (short needles), m. p. 119—120°, was regarded as the *threo*-form (Found : 71·4; H, 7·15; N, 4·6. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·10; N, 4·7%). The second (0·1 g.) (rhombs), m. p. 167—168°, was regarded as the *erythro*-form (Found : C, 72·1; H, 7·4; N, 5·0%).

(*b*) Hydrogenation of the propiophenone (5·95 g.) in methanol in presence of Raney nickel gave, on fractional crystallisation from methanol, the *erythro*-form (1·6 g.), m. p. 166—168°,

and the *threo*-form (0·84 g.), m. p. 117°. Neither of these gave a depression in m. p. when mixed with the corresponding diol obtained as in (*a*).

Hydrolyses of the Acetamido-diols and Dichloroacetylation of the Bases obtained.—The *erythro*-acetamido-diol (1·5 g.), m. p. 168°, was refluxed for 2½ hr. with 2N-sulphuric acid (15 c.c.). DL-erythro-2-*Amino*-1-p-*benzylphenylpropane*-1 : 3-*diol sulphate* (1·1 g.), plates, m. p. 230—234°, was isolated on cooling and crystallised from dilute sulphuric acid (Found: C, 63·1; H, 6·7; N, 4·4. $C_{16}H_{19}O_2N,\frac{1}{2}H_2SO_4$ requires C, 62·7; H, 6·6; N, 4·6%). The free *base* was obtained, by treatment of the sulphate with sodium hydroxide solution followed by extraction with ethyl acetate and crystallisation from ether, as needles, m. p. 110—114° (Found: N, 5·5. $C_{16}H_{19}O_2N$ requires N, 5·4%). The base (1 g.) was converted into the dichloroacetyl derivative by an excess of methyl dichloroacetate in methanol on the steam-bath (90 min.); after cooling, a crystalline product was isolated by filtration and washed with ether. The solid, dissolved in ethyl acetate, was washed to neutrality with dilute hydrochloric acid and finally with water. The *dichloracetamido*-derivative crystallised from ethyl acetate as plates, m. p. 140—140·5° (Found: C, 58·7; H, 4·9; N, 4·1. $C_{18}H_{19}O_3NCl_2$ requires C, 58·7; H, 5·2; N, 3·8; Cl, 9·3%). The threo-*dichloracetamido*-derivative, obtained in a similar manner but without isolation of the sulphate or base, crystallised from water as needles, m. p. 110° (Found: C, 58·8; H, 5·34; N, 2·8; Cl, 18·7%).

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*Thiophen Derivatives of Biological Interest. Part V.** 2-*Styrylthiophen*, 1 : 2-*Diaryl*-1-2′-*thienylethylenes, and Similar Compounds.*

By NG. H. NAM, NG. PH. BUU-HOÏ, and NG. D. XUONG.

[Reprint Order No. 4869.]

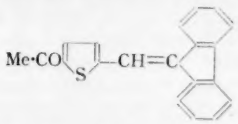
The behaviour of 2-styrylthiophen and of a series of 1 : 2-diaryl-1-2′-thienylethylenes and similar compounds towards formylation with *N*-methylformanilide, Friedel–Crafts acylations, and bromination is investigated. It is shown that, unlike their aromatic analogues, the thiophen derivatives are highly reactive. The bromo-compounds, aldehydes, ketones, thiosemicarbazones, and 4-oxo-Δ^2-thiazolin-2-ylhydrazones obtained in this study are of biological interest. The relation between the electronic structure and reactivity of several molecules in this series is discussed.

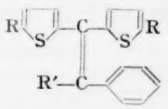
IT has been demonstrated both experimentally, and by wave-mechanical calculations of π-electron densities, that in molecules such as stilbene and 1 : 1 : 2-triphenylethylene the reactivity is shifted from the benzene rings to the external double bond (cf. Buu-Hoï and Royer, *J.*, 1948, 1078; Daudel *et al.*, *Rev. Sci.*, **1946**, **84**, 489; *Compt. rend.*, 1946, **223**, 947; Daudel and Pullman, *J. Phys. Radium*, 1946, **59**, 74, 105; Coulson and Daudel, *Rev. Sci.*, 1947, **85**, 29; Buu-Hoï *et al.*, *ibid.*, p. 1041). Thus, stilbene undergoes Friedel–Crafts acetylation with great difficulty (Ross, *J.*, 1945, 536), and halogenation and nitration of 1 : 1 : 2-triphenylethylene result only in the 2-bromo-, 2-chloro-, and 2-nitro-derivatives (Meisenheimer, *Annalen*, 1927, **456**, 126; Bergmann and Bondt, *Ber.*, 1931, **64**, 1455; Bergmann, Dimant, and Japhe, *J. Amer. Chem. Soc.*, 1948, **70**, 1618). It was therefore of interest to examine the reactivity of analogues of stilbene and 1 : 1 : 2-triphenylethylene in which one or more benzene nuclei would be replaced by the more reactive thiophen. A further incentive lay in the possible biological value of these thiophen compounds and their derivatives (cf. Buu-Hoï *et al.*, *Compt. rend.*, 1945, **220**, 175; Corre *et al.*, *Bull. Soc. Chim. biol.*, 1946, **28**, 716; 1948, **30**, 674; Robson, Davies, and Tebrich, *Brit. J. Pharmacol.*, 1950, **5**, 376).

The reactions studied in the present work were: phosphorus oxychloride-catalysed

* Part IV, *J.*, 1953, 547.

aldehyde syntheses by means of *N*-methylformanilide and *N*-dimethylformamide; stannic chloride-catalysed Friedel–Crafts ketone syntheses; and halogenation with free bromine. 2-Styrylthiophen was smoothly converted into 2-formyl-5-styrylthiophen under the usual conditions for the synthesis of aldehydes of alkylthiophens (cf. King and Nord, *J. Org. Chem.*, 1948, **13**, 635; Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130); the constitution of this aldehyde was established by Kishner–Wolff reduction to the known 5-methyl-2-styrylthiophen (Buu-Hoï *et al.*, *loc. cit.*, 1950). Friedel–Crafts condensation of 2-styrylthiophen with acetyl and propionyl chloride in the presence of stannic chloride afforded excellent yields of 2-acetyl- and 2-propionyl-5-styrylthiophen, the constitution of the former ketone being similarly determined by reduction to 2-ethyl-5-styrylthiophen, which was independently prepared from 2-ethyl-5-formylthiophen and benzylmagnesium chloride, the resulting alcohol being dehydrated by formic acid. These experiments revealed the outstanding reactivity of the 5-position in the molecule of 2-styrylthiophen, as compared with stilbene which was totally inert in the same reactions. A similar reactivity was shown by 1 : 2-diphenyl-1-2′-thienylethylene, which was readily converted into the 5-acetyl-2-thienyl, 5-propionyl-2-thienyl, and 5-benzoyl-2-thienyl compounds. The constitution of the first-named ketone was determined by reduction to 1 : 2-diphenyl-1-(5-ethyl-2-thienyl)-ethylene, which was prepared separately from 2-benzoyl-5-ethylthiophen and benzylmagnesium chloride, with dehydration of the intermediate alcohol by formic acid. This behaviour was not substantially affected by the presence of halogen atoms or methyl or methoxy-groups in *para*-position on either or both of the benzene nuclei, and all these substituted ethylenes yielded ketones which, together with their derivatives, are listed in the Table. 9-2′-Thenylidenefluorene also readily underwent Friedel–Crafts acetylation, to give 9-(5-acetyl-2-thenylidene)fluorene (I); in the case of 2-phenyl-1 : 1-di-2′-thienylethylene, in whose molecule there are two thiophenic 5-positions free, a diketone (II; R = COMe, R′ = H) was obtained.

(I) 



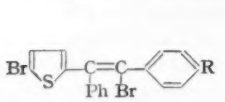
(II)

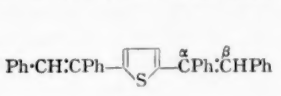
Formylation of thienyldiarylethylenes by means of *N*-methylformanilide could be effected in all instances. In the case of 2-*p*-chlorophenyl-1-phenyl-1-2′-thienylethylene, the corresponding aldehyde was obtained as a well-crystallised substance; for the other ethylenes, the aldehydes were characterised as their semicarbazones and 2 : 4-dinitrophenylhydrazones.

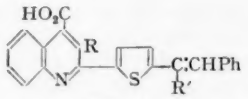
Bromination of 1 : 2-diphenyl-1-2′-thienylethylene with one or two molecules of halogen yielded a dibromo-compound which was identical with the monobromination product of 1 : 2-diphenyl-1-(5-bromo-2-thienyl)ethylene, and was therefore probably 1-bromo-2-(5-bromo-2-thienyl)-1 : 2-diphenylethylene (III; R = H); this structure is upheld by the results of bromination of a series of similar ethylenes with one thiophenic 5-position free and bearing additional halogen, methyl, or methoxy-substituents in the phenyl nuclei, all of which gave dibromo-derivatives. This behaviour confirms previous observations (Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1948, **67**, 309; 1949, **68**, 441) on the bromination of diarylthienylethylenes with no thiophenic 5-positions free, which resulted in monobrominated compounds; it was therefore to be expected that 2-phenyl-1 : 1-di-2′-thienylethylene (II; R = R′ = H) would give a trisubstituted derivative with bromine, and this was in fact the case, the compound obtained being probably 2-bromo-1 : 1-di-(5-bromo-2-thienyl)-2-phenylethylene (II; R = R′ = Br). It thus appears that in the molecule of 1 : 2-diphenyl-1-2′-thienylethylene, the thiophenic 5-position is the most reactive in formylation and Friedel–Crafts acylations, and shares this property with the free position on the ethylene bond as regards bromination; this is in line with theoretical considerations, which assign high π-electron densities to the 2- and the 5-position in the thiophen nucleus.

In view of the known hepatotoxic effects of 2-arylcinchoninic acids, some similar compounds were prepared by Pfitzinger reaction on methyl ketones derived from 2-styrylthiophen

and diarylthienylethylenes, for biological testing. Whereas 5-propionyl-2-styrylthiophen readily underwent a similar reaction, 1 : 2-diphenyl-1-(5-propionyl-2-thienyl)ethylene failed to do so under the same experimental conditions; similar lack of reactivity of ketones bearing bulky substituents in the *para*-position had already been observed in the benzene series (De Clercq and Buu-Hoï, *Compt. rend.*, 1948, **227**, 1377).


(III)


(IV)


(V)

Replacement of a benzene by a thiophen nucleus in the fully conjugated polyarylethylenes is accompanied by an important bathochromic effect, shown, *e.g.*, in the yellow colour of 9-2′-thenylidenefluorene in contrast to colourless stilbene; similarly, the semicarbazones of the aldehydes and ketones described above are yellow, and the thiosemicarbazones and 4-oxo-Δ^2-thiazolin-2-ylhydrazones (cf. Buu-Hoï, Hoán, and Lavit, *J.*, 1952, 4590) are yellow to orange-yellow, in contrast to the corresponding purely aromatic compounds which are practically colourless. In this connection, it is interesting to note the orange-yellow colour of 2 : 5-di-α-stilbenylthiophen (IV), a highly conjugated compound prepared from benzylmagnesium chloride and 1-(5-benzoyl-2-thienyl)-1 : 2-diphenylethylene. A spectroscopic analysis of these observations will be published later.

In view of the pronounced tuberculostatic properties of thiosemicarbazones of 5-substituted thenaldehydes (Welsch, Buu-Hoï, Dechamps, Hoán, Le Bihan, and Binon, *Compt. rend.*, 1951, **232**, 1608), the activity against *Mycobacterium tuberculosis var. hominis* (H 37, Rv strain) *in vitro* of the thiosemicarbazones prepared has been determined. When Dubos–Davis " Tween 80 "–albumin medium was used, and the readings taken after 3 weeks at 37°, the annexed results were obtained, showing the decrease in activity corresponding to the increase in bulk of substituents.

Thiosemicarbazone of	Active concn.
2-Formyl-5-styrylthiophen	$1 : 10^5$
2-Acetyl-5-styrylthiophen	$1 : 10^5$
2-*p*-Chlorostyryl-5-formylthiophen	$1 : 10^5$
1-(5-Formyl-2-thienyl)-1 : 2-diphenylethylene	$1 : 10^4$
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-phenylethylene	$1 : 10^4$
1(5-Acetyl-2-thienyl)-1 : 2-diphenylethylene	$1 : 10^3$
1-(5-Acetyl-2-thienyl)-2-phenyl-1-*p*-tolylethylene	$1 : 10^3$
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-phenylethylene	$1 : 10^3$

Experimental

2-Formyl-5-styrylthiophen.—To a solution of 2-styrylthiophen (9·3 g.) and dimethylformamide (4·4 g.) in *o*-dichlorobenzene (15 c.c.), phosphorus oxychloride (9·2 g.) was added, and the mixture cautiously warmed on the water-bath until an exothermic reaction set up; when this had subsided, the mixture was heated for a further hour, then treated with saturated aqueous sodium acetate, and the solvent removed in steam. The residue was taken up in benzene, dried (Na_2SO_4), and purified by vacuum-distillation to yield *2-formyl-5-styrylthiophen* (9·7 g., 90%), b. p. 208—210°/1 mm., which crystallised as shiny, pale yellow needles, m. p. 84°, from methanol (Found: C, 73·6; H, 4·7. $C_{13}H_{10}OS$ requires C, 72·9; H, 4·7%). The corresponding *semicarbazone* crystallised as pale yellow leaflets, m. p. 269—271° (decomp.), from ethanol–benzene (Found: N, 15·3. $C_{14}H_{13}ON_3S$ requires N, 15·5%); the *thiosemicarbazone* formed shiny yellow needles, m. p. 186—187°, from ethanol (Found: N, 14·4. $C_{14}H_{13}N_3S_2$ requires N, 14·6%); the *4-oxo-Δ^2-thiazolin-2-ylhydrazone*, prepared by heating a solution of the thiosemicarbazone (1·2 g.), chloroacetic acid (1·6 g.), and sodium acetate (1·4 g.) in ethanol for 1 hr., crystallised as greenish-yellow prisms, m. p. 296—298° (decomp.), from acetic acid (Found: N, 12·7. $C_{16}H_{13}ON_3S_2$ requires N, 12·8%).

2-Methyl-5-styrylthiophen.—A mixture of the foregoing aldehyde (8·5 g.), 85% hydrazine hydrate (12 g.), and diethylene glycol (60 c.c.) was heated at 100° for 5 min.; after addition of potassium hydroxide (12 g.), the mixture was heated with removal of water up to 190—200° and refluxed for 3 hr. Dilute hydrochloric acid was added after cooling, and the product taken

up in benzene and purified by vacuum-distillation; 2-methyl-5-styrylthiophen (6·8 g., 85% yield) had b. p. 155—157°/0·8 mm., and crystallised from ethanol as colourless leaflets, m. p. 85° (cf. Buu-Hoï, Hoán, and Lavit, *loc. cit.*, 1950).

2-*Acetyl-5-styrylthiophen.*—To an ice-cooled solution of acetyl chloride (7·5 g.) and 2-styrylthiophen (14·9 g.) in dry benzene (150 c.c.), stannic chloride (25 g.) was added during 15 min. with stirring; the dark red mixture was kept at room temperature for 1½ hr. and decomposed with dilute hydrochloric acid. The product gave on vacuum-fractionation a *ketone* (12·8 g., 70%), b. p. 238—240°/13 mm., crystallising as shiny, pale yellow needles, m. p. 134°, from methanol (Found: C, 73·5; H, 5·4. $C_{14}H_{12}OS$ requires C, 73·7; H, 5·3%). The *semicarbazone* formed yellow needles, m. p. 228° (decomp.), from methanol (Found: N, 14·7. $C_{15}H_{15}ON_3S$ requires N, 14·7%); the 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 242° (decomp.), from benzene (Found: N, 13·6. $C_{20}H_{16}O_4N_4S$ requires N, 13·7%).

2-*Ethyl-5-styrylthiophen.*—Wolff–Kishner–Huang-Minlon reduction of 5-acetyl-2-styrylthiophen gave a product which formed a pale yellow oil, b. p. 154—156°/0·6 mm., solidifying to a crystalline mass, m. p. 30° (87% yield); the same *product* was obtained by the reaction of benzylmagnesium chloride with 5-ethyl-2-thenaldehyde in the usual way (Found: C, 78·3; H, 6·5. $C_{14}H_{14}S$ requires C, 78·5; H, 6·5%).

2-*Propionyl-5-styrylthiophen.*—Obtained in 70% yield from 2-styrylthiophen (14·9 g.), propionyl chloride (8·9 g.), and stannic chloride (25 g.) in benzene (150 c.c.), this *ketone* had b. p. 253—254°/13 mm., and formed pale yellow needles, m. p. 108°, from methanol (Found: C, 74·2; H, 6·0. $C_{15}H_{14}OS$ requires C, 74·4; H, 5·8%); the *semicarbazone* formed yellow needles, m. p. 216—217° (decomp.) (Found: N, 13·9. $C_{16}H_{17}ON_3S$ requires N, 14·0%). 2-*Benzoyl-5-styrylthiophen*, similarly prepared in 55% yield from benzoyl chloride, had b. p. 238—239°/0·5 mm., and formed greenish-yellow leaflets, m. p. 116° (Found: C, 78·0; H, 5·1. $C_{19}H_{14}OS$ requires C, 78·6; H, 4·8%).

3-*Methyl*-2-(5-*styryl*-2-*thienyl*)*cinchoninic Acid* (V; R = Me, R′ = H).—A mixture of 2-propionyl-5-styrylthiophen (2·5 g.), isatin (1·8 g.), and potassium hydroxide (2·3 g.) in ethanol (30 c.c.) was refluxed for 24 hr.; water was added, and the aqueous solution extracted with ether and acidified with acetic acid. The *acid* (2·5 g.) crystallised as yellow prisms, m. p. 268° (decomp.), from ethanol (Found: C, 74·2; H, 4·4. $C_{23}H_{17}O_2NS$ requires C, 74·4; H, 4·6%).

9-2′-*Thenylidenefluorene.*—Sodium (10·1 g.) was treated with absolute ethanol (500 c.c.), and to this solution fluorene (37·5 g.) was added, and the mixture heated on the water-bath until the hydrocarbon had completely dissolved; 2-thenaldehyde (22·4 g.) was then added dropwise with stirring, and the mixture kept for 1 hr. at 75—80°, and overnight at room temperature. The residue from distillation of the ethanol was treated with dilute sulphuric acid, and the product taken up in benzene and purified by vacuum-distillation. 9-2′-*Thenylidenefluorene*, obtained in 63% yield, formed from ethanol greenish-yellow needles, m. p. 72°, and gave a blood-red colour in sulphuric acid (Found: C, 83·1; H, 4·6. $C_{18}H_{12}S$ requires C, 82·9; H, 4·6%).

9-(5-*Acetyl*-2-*thenylidene*)*fluorene* (III).—To a cooled solution of 9-2′-thenylidenefluorene (13 g.) and acetyl chloride (4·7 g.) in benzene (200 c.c.), stannic chloride (15·6 g.) was added portionwise with stirring, and the mixture kept for 75 min. at room temperature. After the usual treatment, the ketone obtained in 82% yield formed orange-yellow needles, m. p. 116°, from ethanol (Found: C, 79·6; H, 4·6. $C_{20}H_{14}OS$ requires C, 79·5; H, 4·6%). The *oxime* formed yellow prisms, m. p. 166°, from ethanol (Found: N, 4·4. $C_{20}H_{15}ONS$ requires N, 4·4%); the *semicarbazone* formed yellow prisms, m. p. 257° (decomp.), from ethanol–benzene (Found: N, 11·6. $C_{21}H_{17}ON_3S$ requires N, 11·7%); the 2 : 4-*dinitrophenylhydrazone* formed crimson needles, m. p. 278° (decomp.), from nitrobenzene (Found: N, 11·6. $C_{26}H_{18}O_4N_4S$ requires N, 11·6%). An attempt to perform a Pfitzinger reaction with isatin and this ketone failed on account of resinification.

1-(5-*Bromo*-2-*thienyl*)-1 : 2-*diphenylethylene.*—To an ethereal solution of benzylmagnesium chloride (from 4·8 g. of magnesium and 25·3 g. of benzyl chloride) a solution of 2-benzoyl-5-bromothiophen (26·7 g.) (cf. Buu-Hoï, Hoán, and Xuong, *Rec. Trav. chim.*, 1950, **69**, 1083) in ether (250 c.c.) was added portionwise, and the mixture refluxed on the water-bath for 15 min. The crude alcohol obtained on decomposition with dilute sulphuric acid was heated for 5 min. with 99% formic acid (60 g.), the mixture poured into water, and the *ethylene* formed taken up in benzene and vacuum-distilled. It formed a thick, pale yellow oil (29·5 g. 86%), b. p. 192—194°/0·5 mm., n_D^{25} 1·6887, giving an orange colour in sulphuric acid (Found: C, 63·0; H, 3·9. $C_{18}H_{13}SBr$ requires C, 63·3; H, 3·8%).

1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1 : 2-*diphenylethylene* (III; R = H).—(*a*) To an ice-cooled solution of the foregoing ethylene (3·4 g.) in acetic acid (20 c.c.), bromine (1·6 g. in 20 c.c. of

acetic acid) was added portionwise with stirring, and the mixture kept for ½ hr. at room temperature; the precipitate obtained was collected, washed with water, and crystallised as colourless needles (3 g.), m. p. 127°, from acetic acid (Found: C, 51·6; H, 2·8; Br, 37·9. $C_{18}H_{12}SBr_2$ requires C, 51·4; H, 2·9; Br, 38·1%).

(*b*) A solution of 1 : 2-diphenyl-1-2′-thienylethylene (2·6 g.) in cold acetic acid (20 c.c.) was treated in the same way with bromine (2·9 g. in 20 c.c. of acetic acid); the product obtained was identical with the above.

1-p-*Chlorophenyl*-2-*phenyl*-1-2′-*thienylethylene*.—Prepared in 75% yield from benzylmagnesium chloride (from 17·7 g. of benzyl chloride and 3·4 g. of magnesium in 100 c.c. of ether) and 2-*p*-chlorobenzoylthiophen (15·6 g.; cf. Buu-Hoï, Hoán, and Xuong, *loc. cit.*), the *ethylene* formed colourless prisms, m. p. 78°, b. p. 243—244°/12 mm., from methanol (Found: C, 72·8; H, 4·4; Cl, 11·9. $C_{18}H_{13}SCl$ requires C, 72·8; H, 4·4; Cl, 12·0%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-2-p-*chorophenyl*-1-*phenylethylene*, obtained from the foregoing ethylene with bromine, formed colourless prisms, m. p. 124°, from acetic acid (Found: C, 47·7; H, 2·5. $C_{18}H_{11}SBr_2Cl$ requires C, 47·5; H, 2·4%).

1-p-*Bromophenyl*-2-*phenyl*-1-2′-*thienylethylene*.—Prepared in 86% yield from 2-*p*-bromobenzoylthiophen (26·7 g.; cf. Buu-Hoï, Hoán, and Xuong, *loc. cit.*) and benzylmagnesium chloride (from 25·3 g. of benzyl chloride and 4·8 g. of magnesium), this *compound* formed colourless prisms, m. p. 108°, from methanol; it gave a dark orange colour in sulphuric acid (Found: C, 63·2; H, 3·9; Br, 23·3. $C_{18}H_{13}SBr$ requires C, 63·3; H, 3·8; Br, 23·5%). 2-*Bromo*-1-p-*bromophenyl*-1-(5-*bromo*-2-*thienyl*)-2-*phenylethylene* formed colourless prisms, m. p. 149°, from acetic acid (Found: C, 43·0; H, 2·1; Br, 47·8. $C_{18}H_{11}SBr_3$ requires C, 43·3; H, 2·2; Br, 48·1%).

2-p-*Chlorophenyl*-1-*phenyl*-1-2′-*thienylethylene*.—Prepared in 89% yield from 2-benzoylthiophen (62 g.) and *p*-chlorobenzylmagnesium chloride (from 12·7 g. of magnesium and 85·5 g. of *p*-chlorobenzyl chloride in 400 c.c. of ether), this *product* formed colourless prisms, m. p. 64°, b. p. 237—238°/12 mm., from methanol; it gave an orange colour with sulphuric acid (Found: C, 72·8; H, 4·5; Cl, 11·9%). 2-*Bromo*-1-(5-*bromo*-2-*thienyl*)-2-p-*chlorophenyl*-1-*phenylethylene* (III; R = Cl) formed colourless needles, m. p. 148° (Found: C, 47·5; H, 2·5%).

2-p-*Toluoylthiophen*.—To an ice-cooled solution of thiophen (25·2 g.) and *p*-toluoyl chloride (38·6 g.) in benzene (200 c.c.), stannic chloride (78 g.) was added during 45 min. with stirring; the mixture was kept for 2 hr. at room temperature, and worked up in the usual way, the *ketone* (45 g., 89%), b. p. 196—197°/14 mm., crystallising as colourless needles, m. p. 72°, from methanol (Found: C, 71·3; H, 5·0. $C_{12}H_{10}OS$ requires C, 71·3; H, 5·0%).

2-*Phenyl*-1-2′-*thienyl*-1-p-*tolylethylene*.—Prepared in 88% yield from 2-*p*-toluoylthiophen (20·1 g.) and benzylmagnesium chloride (from 4·8 g. of magnesium and 25·3 g. of benzoyl chloride in 150 c.c. of ether) this *stilbene* derivative formed colourless leaflets, m. p. 61°, b. p. 206—207°/0·6 mm., from methanol (Found: C, 82·5; H, 5·8. $C_{19}H_{16}S$ requires C, 82·6; H, 5·8%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-*phenyl*-2-*p*-*tolylethylene* formed colourless needles, m. p. 134°, from acetic acid (Found: C, 52·5; H, 3·2; Br, 36·7. $C_{19}H_{14}SBr_2$ requires C, 52·5; H, 3·2; Br, 36·9%).

1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-2-p-*methoxyphenyl*-1-*phenylethylene*, prepared from 1-*p*-methoxyphenyl-2-phenyl-1-2′-thienylethylene (Buu-Hoï, Hoán, and Xuong, *loc. cit.*) with bromine, formed colourless needles, m. p. 120°, from acetic acid (Found: C, 50·8; H, 3·2; Br, 35·4. $C_{19}H_{14}OSBr_2$ requires C, 50·7; H, 3·1; Br, 35·5%).

2-p-*Chlorophenyl*-1-2′-*thienyl*-1-p-*tolylethylene*, prepared in 86% yield from 2-*p*-toluoylthiophen (18·2 g.) and *p*-chlorobenzylmagnesium chloride (from 3·6 g. of magnesium and 24·5 g. of *p*-chlorobenzyl chloride in 200 c.c. of ether), formed colourless needles, m. p. 76°, b. p. 212—213°/0·5 mm., from methanol and gave an orange-red colour with sulphuric acid (Found: C, 73·5; H, 4·7; Cl, 11·4. $C_{19}H_{15}SCl$ requires C, 73·4; H, 4·8; Cl, 11·4%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-p-*chlorophenyl*-2-p-*tolylethylene* formed colourless needles, m. p. 161°, from acetic acid (Found: C, 48·7; H, 2·9. $C_{19}H_{13}SBr_2Cl$ requires C, 48·7; H, 2·8%).

2-p-*Chlorophenyl*-1-p-*methoxyphenyl*-1-2′-*thienylethylene*, prepared in 94% yield from 2-*p*-anisoylthiophen (32·7 g.) and *p*-chlorobenzylmagnesium chloride (from 38·7 g. of *p*-chlorobenzyl chloride and 5·8 g. of magnesium), formed silky colourless needles, m. p. 112°, b. p. 230—231°/0·6 mm., from methanol (Found: C, 69·9; H, 4·6; Cl, 10·7. $C_{49}H_{15}OSCl$ requires C, 69·8; H, 4·6; Cl, 10·9%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-p-*chlorophenyl*-2-p-*methoxyphenylethylene* formed colourless prisms, m. p. 150°, from acetic acid (Found: C, 47·2; H, 2·8. $C_{19}H_{13}OSBr_2Cl$ requires C, 47·0; H, 2·7%).

2-*Bromo*-1 : 1-*di*-(5-*bromo*-2-*thienyl*)*ethylene* (II; R = R′ = Br), obtained from 2-phenyl-1 : 1-di-2′-thienylethylene (Buu-Hoï and Hoán, *loc. cit.*) and 3 mol. of bromine in acetic acid,

Ketones[a] *and aldehydes*[b] *derived from* 1 : 2-*diaryl*-1-2′-*thienylethylenes.*

Ethylene derivative	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
1-(5-Acetyl-2-thienyl)-1 : 2-diphenyl	112°	$C_{20}H_{16}OS$	78·9	5·4	78·9	5·3
oxime	201	$C_{20}H_{17}ONS$	N, 4·3		N, 4·4	
semicarbazone	200 *	$C_{21}H_{19}ON_3S$	N, 11·4		N, 11·6	
thiosemicarbazone	196	$C_{21}H_{19}N_3S_2$	66·7	4·9	66·8	5·0
2 : 4-dinitrophenylhydrazone	229	$C_{26}H_{20}O_4N_4S$	N, 11·4		N, 11·6	
1-(5-Propionyl-2-thienyl)-1 : 2-diphenyl	78	$C_{21}H_{18}OS$	79·4	5·7	79·2	5·7
oxime	174	$C_{21}H_{19}ONS$	N, 4·0		N, 4·2	
semicarbazone	170 *	$C_{22}H_{21}ON_3S$	N, 11·1		N, 11·2	
1-(5-Benzoyl-2-thienyl)-1 : 2-diphenyl	123	$C_{25}H_{18}OS$	81·9	4·9	82·0	4·9
oxime	182	$C_{25}H_{19}ONS$	N, 3·5		N, 3·7	
1-(5-Acetyl-2-thienyl)-1-*p*-chlorophenyl-2-phenyl	120	$C_{20}H_{15}OSCl$	71·0	4·5	70·9	4·4
oxime	221	$C_{20}H_{16}ONSCl$	N, 3·9		N, 4·0	
semicarbazone	211 *	$C_{21}H_{18}ON_3SCl$	N, 10·5		N, 10·5	
2 : 4-dinitrophenylhydrazone	269 *	$C_{26}H_{19}O_4N_4SCl$	N, 10·5		N, 10·8	
1-(5-Acetyl-2-thienyl)-2-phenyl-1-*p*-tolyl	122	$C_{21}H_{18}OS$	79·2	5·8	79·2	5·7
oxime	193	$C_{21}H_{19}ONS$	N, 4·1		N, 4·2	
semicarbazone	238 *	$C_{22}H_{21}ON_3S$	N, 11·1		N, 11·2	
thiosemicarbazone	226 *	$C_{22}H_{21}N_3S_2$	67·5	5·3	67·5	5·4
1-(5-Acetyl-2-thienyl)-1-*p*-methoxyphenyl-2-phenyl	103	$C_{21}H_{18}O_2S$	75·4	5·4	75·4	5·4
oxime	182	$C_{21}H_{19}O_2NS$	N, 4·0		N, 4·0	
semicarbazone	228 *	$C_{22}H_{21}O_2N_3S$	N, 10·7		N, 10·7	
2 : 4-dinitrophenylhydrazone	252	$C_{27}H_{22}O_5N_4S$	N, 10·7		N, 10·9	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-phenyl	105	$C_{20}H_{15}OSCl$	71·1	4·5	70·9	4·4
oxime	199	$C_{20}H_{16}ONSCl$	N, 3·9		N, 4·0	
semicarbazone	214	$C_{21}H_{18}ON_3SCl$	N, 10·5		N, 10·6	
thiosemicarbazone	196 *	$C_{21}H_{18}N_3S_2Cl$	61·0	4·3	61·2	4·4
2-*p*-Chlorophenyl-1-phenyl-1-(5-propionyl-2-thienyl)	92	$C_{21}H_{17}OSCl$	71·4	4·7	71·5	4·8
oxime	147	$C_{21}H_{18}ONSCl$	N, 3·6		N, 3·8	
semicarbazone	187 *	$C_{22}H_{20}ON_3SCl$	N, 10·0		N, 10·2	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-*p*-tolyl-	124	$C_{21}H_{17}OSCl$	71·4	4·9	71·5	4·8
oxime	187	$C_{21}H_{18}ONSCl$	N, 3·7		N, 3·8	
semicarbazone	244 *	$C_{22}H_{20}ON_3SCl$	N, 10·1		N, 10·2	
2 : 4-dinitrophenylhydrazone	262	$C_{27}H_{21}O_4N_4SCl$	N, 10·5		N, 10·5	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-*p*-methoxyphenyl-	100	$C_{21}H_{17}O_2SCl$	68·3	4·6	68·4	4·6
oxime	184	$C_{21}H_{18}O_2NSCl$	N, 3·6		N, 3·6	
semicarbazone	224 *	$C_{22}H_{20}O_2N_3SCl$	N, 9·8		N, 9·9	
2 : 4-dinitrophenylhydrazone	253 *	$C_{27}H_{21}O_5N_4SCl$	N, 10·1		N, 10·2	
1 : 1-Di-(5-acetyl-2-thienyl)-2-phenyl[c]	169	$C_{20}H_{16}O_2S_2$	68·3	4·6	68·2	4·5
disemicarbazone	>310	$C_{22}H_{22}O_2N_6S_2$	N, 17·8		N, 18·0	
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-phenyl-	114	$C_{19}H_{13}OSCl$	70·1	4·3	70·3	4·0
oxime	164	$C_{19}H_{14}ONSCl$	N, 4·0		N, 4·1	
semicarbazone	240—242	$C_{20}H_{16}ON_3SCl$	N, 10·9		N, 11·1	
thiosemicarbazone	212 *	$C_{20}H_{16}N_3S_2Cl$	60·2	3·9	60·4	4·0
4-oxo-Δ^3-thiazolin-2-ylhydrazone	272—274	$C_{22}H_{16}ON_3S_2Cl$	N, 9·4		N, 9·6	
2 : 4-dinitrophenylhydrazone	266 *	$C_{25}H_{17}O_4N_4SCl$	N, 10·8		N, 11·1	
1-(5-Formyl-2-thienyl)-1 : 2-diphenylethylene	B. p. 209—210°/0·7 mm.	—	—		—	
semicarbazone	220—221 *	$C_{20}H_{17}ON_3S$	N, 11·9		N, 12·1	
2 : 4-dinitrophenylhydrazone	232 *	$C_{25}H_{18}O_4N_4S$	N, 11·7		N, 11·9	
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-*p*-methoxyphenyl-	B. p. 258—260°/0·6 mm.	—	—		—	
semicarbazone	199—200	$C_{21}H_{18}O_2N_3SCl$	N, 10·0		N, 10·2	

[a] The ketones, prepared as for 9-(2-thenylidene)fluorene, were recrystallised from methanol and were pale yellow; the corresponding oximes, semicarbazones, and thiosemicarbazones, recrystallised from ethanol, were yellow or orange-yellow, and the 2 : 4-dinitrophenylhydrazones (toluene) were red. [b] The pale yellow aldehydes were prepared from the appropriate ethylene, phosphorus oxychloride, and *N*-methylformanilide or dimethylformamide, as for formylation of 2-styrylthiophen; the oximes and 4-oxo-Δ^2-thiazolin-2-ylhydrazones were yellow, the semicarbazones and thiosemicarbazones orange-yellow, and the 2 : 4-dinitrophenylhydrazones red. Recrystallisation from ethanol (oximes, semicarbazones, thiosemicarbazones) or acetic acid or toluene (4-oxo-Δ^2-thiazolin-2-ylhydrazones and 2 : 4-dinitrophenylhydrazones). [c] This ketone (b. p. 259—261°/0·3 mm.) was orange-yellow, its semicarbazone yellow. * With decomp.

formed colourless prisms, m. p. 74° (Found: C, 37·9; H, 1·9; Br, 47·0. $C_{16}H_9S_2Br_3$ requires C, 38·0; H, 1·8; Br, 47·5%).

2-β-*Naphthoylthiophen.*—Prepared in 75% yield from β-naphthoyl chloride (38·1 g.), thiophen (20·2 g.) and stannic chloride (62·8 g.) in benzene (300 c.c.) in the usual way, except that the mixture was kept for 4 hr. at room temperature, the *ketone* crystallised as colourless leaflets, m. p. 89°, from methanol (Found: C, 75·6; H, 4·0. $C_{15}H_{10}OS$ requires C, 75·6; H, 4·2%).

1-β-*Naphthyl*-2-*phenyl*-1-2′-*thienylethylene*, prepared from the foregoing ketone (23·8 g.) and benzylmagnesium chloride (from 25·3 g. of benzyl chloride and 4·8 g. of magnesium in 150 c.c. of ether), formed colourless needles, m. p. 95° (Found: C, 84·4; H, 5·0. $C_{22}H_{16}S$ requires C, 84·6; H, 5·1%).

9-(5-*Acetyl*-2-*thenylidene*)*fluorene.*—To an ice-cooled solution of 9-2′-thenylidenefluorene (13 g.) and acetyl chloride (4·7 g.) in benzene (200 c.c.), stannic chloride (15·6 g.) was added portionwise with stirring; the mixture was kept for 75 min. at room temperature, and worked up in the usual way, to yield 82% of a *ketone*, b. p. 270—272°/0·6 mm., forming orange-yellow needles, m. p. 115°, from ethanol (Found: C, 79·6; H, 4·6. $C_{20}H_{14}OS$ requires C, 79·5; H, 4·6%). The *oxime* crystallised as yellow prisms, m. p. 165°, from ethanol (Found: N, 4·4. $C_{20}H_{15}ONS$ requires N, 4·4%); the *semicarbazone* formed yellow needles, m. p. 257° (decomp.), from ethanol–benzene (Found: N, 11·5. $C_{21}H_{17}ON_3S$ requires N, 11·7%).

1-(5-*Ethyl*-2-*thienyl*-1 : 2-*diphenylethylene.*—(a) *By reduction of* 1-(5-*acetyl*-2-*thienyl*)-1 : 2-*diphenylethylene*. This ketone (9·1 g.), on reduction in the usual way with 85% hydrazine hydrate (15 g.) and potassium hydroxide (15 g.) in diethylene glycol (80 c.c.), gave the *stilbene* derivative as a pale yellow oil (8 g.), b. p. 187—188°/0·5 mm., n_D^{25} 1·6667 (Found: C, 82·6; H, 6·1. $C_{20}H_{18}S$ requires C, 82·7; H, 6·2%). (b) *By Grignard synthesis.* The same product was obtained in 75% yield from benzylmagnesium chloride (25·3 g. of benzyl chloride and 4·8 g. of magnesium in 200 c.c. of ether) and 2-benzoyl-5-ethylthiophen.

2 : 5-*Di*-α-*stilbenylthiophen* (IV).—To a cooled Grignard reagent made from benzyl chloride (7·6 g.) and magnesium (1·45 g.) in ether (100 c.c.), a solution of 1-(5-benzoyl-2-thienyl)-1 : 2-diphenylethylene (11 g.) in dry benzene (100 c.c.) was added portionwise, and the mixture refluxed for 15 min. on the water-bath. After decomposition with dilute sulphuric acid, the alcohol obtained was dehydrated with 98% formic acid (20 g.), and the product vacuum-fractionated. The *ethylene* (71%), b. p. 290—292°/0·8 mm., forming orange-yellow needles, m. p. 142°, from acetic acid (Found: C, 86·8; H, 5·3. $C_{32}H_{24}S$ requires C, 87·3; H, 5·4%). This compound was highly sensitive to oxygen and light and gave a deep violet colour in sulphuric acid.

2-(5-α-*Stilbenyl*-2-*thienyl*)*cinchoninic Acid* (V; R = H, R′ = Ph).—A mixture of 1-(5-acetyl-2-thienyl)-1 : 2-diphenylethylene (3 g.), isatin (1·8 g.), and potassium hydroxide (2·2 g.) in ethanol (15 c.c.) was refluxed for 24 hr.; the precipitate obtained on dilution with water, ether-extraction, and acidification with acetic acid formed yellow prisms, m. p. 225—226° (decomp.), from ethanol (Found: C, 77·3; H, 4·6. $C_{28}H_{19}O_2NS$ requires C, 77·6; H, 4·4%). 1 : 2-Diphenyl-1-(5-propionyl-2-thienyl)ethylene, treated in the same way with isatin, was recovered unchanged even after 48 hours' heating.

Various.—Other *compounds* prepared are listed in the Table.

Thanks are offered to Prof. M. Welsch, Bacteriological Institute, University of Liége, for having tested the compounds for tuberculostatic activity. Results of biological tests for œstrogenic and progesterone-like activity will be reported elsewhere.

The Radium Institute, University of Paris. [*Received, December 7th*, 1953.]

Internuclear Cyclisation. Part VIII. Naphth*[3 : 2 : 1-cd]*oxindoles.*

By R. A. Abramovitch and D. H. Hey.

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The condensation of *o*-nitrobenzaldehyde with oxindole gives 3-*o*-nitrobenzylideneoxindole, which on successive reduction, diazotisation, and decomposition of the diazonium solution with copper powder gives naphth[3 : 2 : 1-*cd*]oxindole. This sequence of reactions is further exemplified by the use of (*a*) benzo-substituted oxindoles, (*b*) substituted *o*-nitrobenzaldehydes, and (*c*) *N*-phenyloxindole. An attempt to apply the same reaction to thio-oxindole gave 3-*o*-mercaptophenylcarbostyril. Condensation of quinoline-2-aldehyde with oxindole gives the same product as is obtained from isatin and quinaldine, and similar condensation reactions of isatin with α-picoline, 4-hydroxyquinaldine, and 3-nitroquinaldine are reported. An improved general method for the preparation of oxindoles is described.

Among tetracyclic structures which lend themselves to a method of synthesis involving internuclear cyclisation by means of the Pschorr reaction or one of its modifications is the naphth[3 : 2 : 1-*cd*]oxindole system.† The parent substance (III), which appears to be the only known representative of this series, was prepared by Pschorr and Popovici (*Ber.*, 1906, **39**, 3120; see also Kishi, *J. Pharm. Soc. Japan*, 1926, **532**, 475), who reduced *o*-nitro-α-*o*′-nitrophenylcinnamic acid (I), obtained by condensation of *o*-nitrobenzaldehyde with *o*-nitrophenylacetic acid, to 3-*o*-aminobenzylideneoxindole (II), which was then diazotised and decomposed with copper powder to give naphth[3 : 2 : 1-*cd*]oxindole (III). The structure assigned by Pschorr to this compound is not free from ambiguity because the precise stereochemistry of this reduction of *o*-nitro-α-*o*′-nitrophenylcinnamic acid is uncertain. If his amine possessed the structure (II) the identity of his product, m. p. 229°, as naphth[3 : 2 : 1-*cd*]oxindole ($C_{15}H_9ON$) is clearly established; but if a geometrical isomerisation occurred during the reduction, his amine would have the structure (V) derived from the diamine (IV), and this could lead under similar experimental conditions to 3-phenylcarbostyril (VI) ($C_{15}H_{11}ON$), m. p. 228·5°, the small difference in hydrogen content being barely adequate to permit an unequivocal decision between the two. Borsche, Wagner-Roemmich, and Barthenheier (*Annalen*, 1942, **550**, 160) prepared an amine identical in physical properties with that of Pschorr and Popovici (*loc. cit.*) by reduction of 3-*o*-nitrobenzylideneoxindole. This amine was converted into quinindoline (VIII) by the action of heat. Quinindoline can be obtained from the amine (V) as well as from (VII), and in view of the results obtained in the thio-oxindole series (p. 1703), there was a possibility that this amine was 3-*o*-aminophenylcarbostyril (V) and not 3-*o*-aminobenzylideneoxindole (VII).

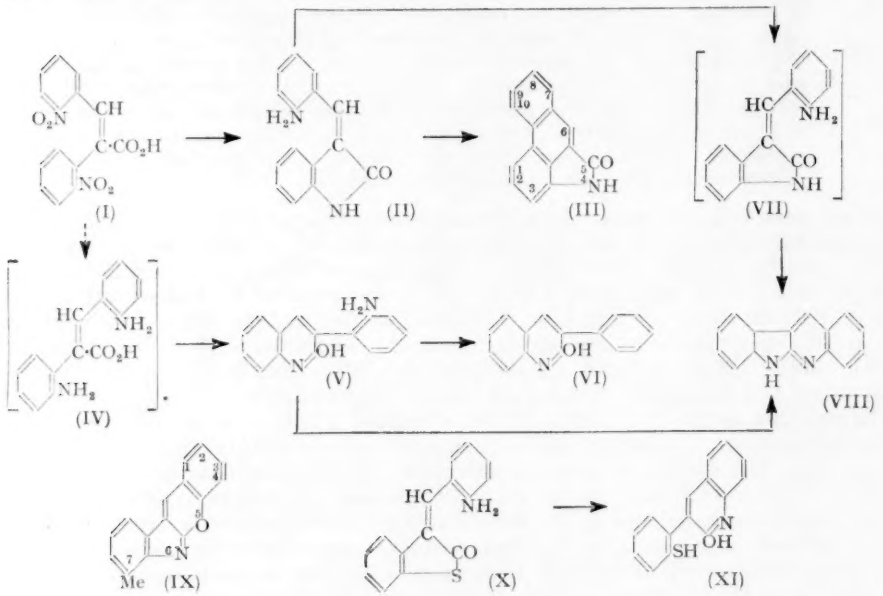
It thus became necessary to establish the structure of Pschorr's naphthoxindole and its amine precursor beyond doubt, and for this purpose it was prepared by the more straightforward route from oxindole by means of 3-*o*-nitrobenzylideneoxindole and 3-*o*-aminobenzylideneoxindole, a general method which was subsequently used for the preparation of further members of the series. The product obtained in this manner was isolated in the form of yellow prisms, m. p. 229°, whereas 3-phenylcarbostyril, m. p. 228·5°, is colourless. A mixed melting point showed a marked depression to 180—185°.

The identity of Pschorr's naphthoxindole and 3-*o*-aminobenzylideneoxindole being established, the general method outlined above was then applied to the synthesis of 3-methyl-, 1-bromo-, 8 : 9-dimethoxy-, 8 : 9-methylenedioxy , 8-chloro-, and 4-phenylnaphth[3 : 2 : 1-*cd*]oxindole. These reactions include examples with a substituent in turn in each of the three ring systems present in the aminobenzylideneoxindole. In addition, an attempt to prepare 1 : 3-dibromonaphth[3 : 2 : 1-*cd*]oxindole led unexpectedly to 3-bromonaphth[3 : 2 : 1-*cd*]oxindole.

For the preparation of oxindoles used as starting compounds an improved method was developed which involved heating the chloroacetanilide in a molten mixture of aluminium

* Part VII, *J.*, 1953, 3. † The method of numbering used in this paper is based on the Ring Index.

chloride and sodium chloride. The reaction is complete within two minutes and gives more satisfactory results than that of Stollé (*J. pr. Chem.*, 1930, **128**, 1). Reduction of the nitrobenzylideneoxindoles was carried out with a solution of stannous chloride in glacial acetic acid containing hydrogen chloride under mild conditions in order to minimise geometric isomerisation. The products from the internuclear cyclisation reaction were worked up with the aid of chromatographic adsorption which revealed a number of by-products.



The decomposition of the diazonium sulphate prepared from 3-*o*-aminobenzylidene-7-methyloxindole gave, in addition to 3-methylnaphth[3 : 2 : 1-*cd*]oxindole, an isomeric compound considered to be 7-methylbenzopyrano[2 : 3-*b*]indolenine (IX) (cf. Täuber, *Ber.*, 1891, **24**, 197; Täuber and Halberstadt, *Ber.*, 1892, **25**, 2745; Cullinane, Davey, and Padfield, *J.*, 1934, 716), and believed to have arisen from partial *cis–trans*-isomerisation of the aminobenzylidenemethyloxindole, and its ultra-violet absorption shows a band at about 320 mμ, which is absent in the naphthoxindoles. That such isomerisation occurs during the preparation of the amine salt prior to diazotisation is indicated by the fact that if higher temperatures were allowed to develop the yield of the benzopyranoindolenine was increased. In the decomposition with copper powder of the diazonium sulphate prepared from 3-*o*-aminobenzylidene-5 : 7-dibromo-oxindole one bromine atom was removed and the product proved to be 3-bromonaphth[3 : 2 : 1-*cd*]oxindole, together with 7-bromo-3-*o*-hydroxybenzylideneoxindole; a similar decomposition effected by the action of heat gave the latter phenol only. Decomposition of the diazonium salt prepared from 3-*o*-aminobenzylidene-5-bromo-oxindole gave 1-bromonaphth[3 : 2 : 1-*cd*]oxindole, which was different from that prepared from the dibromo-derivative which must therefore be 3-bromonaphth[3 : 2 : 1-*cd*]oxindole. It is assumed that the same bromine atom is eliminated during the formation of the phenol.

The decomposition of the diazonium sulphate prepared from 3-6′-aminoveratrylidene-oxindole gave, in addition to 8 : 9-dimethoxynaphth[3: 2 : 1-*cd*]oxindole, 3-veratrylidene-oxindole, m. p. 161—162°, which probably has a *cis*-configuration. It is different from the 3-veratrylideneoxindole, m. p. 210—211°, prepared from oxindole and veratraldehyde, but was converted into it on recrystallisation from acetone.

In an attempt to extend this synthetic route to include the preparation of aza-

derivatives of naphth[3 : 2 : 1-*cd*]oxindole attention was directed to the possible use of isatin, in place of oxindole. It is known that isatin undergoes condensation reactions at the 3-position with compounds containing active methylene groups. In preliminary work it was shown that reaction between α-picoline and isatin in the presence of fused zinc chloride gave 3-α-picolinylideneoxindole. Similar reactions were carried out successfully with quinaldine, 3-nitroquinaldine, and 4-hydroxyquinaldine, the product obtained with quinaldine being identical with that obtained by condensation of quinoline-2-aldehyde with oxindole.

The availability of thio-oxindole by the method of Glauert and Mann (*J.*, 1952, 2127) suggested its use for the preparation of naphthothio-oxindoles. Condensation with *o*-nitrobenzaldehyde gave 3-*o*-nitrobenzylidenethio-oxindole, but reduction of the latter with stannous chloride gave 3-*o*-mercaptophenylcarbostyril (XI), which can arise from a *cis–trans*-isomerisation coupled with the opening of the five-membered ring followed by recyclisation to form the quinoline ring (X) ⟶ (XI).

The data for the absorption spectra of three of the foregoing compounds are given in the accompanying table.

Naphth[3 : 2 : 1-*cd*]oxindole				3-Methylnaphth[3 : 2 : 1-*cd*]-oxindole				7-Methylbenzopyrano[2 : 3-*b*]-indolenine			
$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$
203	37·8	290	18·6	202	31·6	290	20·3	206	23·5	258	51·8
207	42·6	353	5·47	205	33·7	353	6·3	224	50·2	319	22·0
220	49·7	365	5·65	209	34·4	365	6·5				
257·5	40·6	368	5·75	223	37·9	368	6·55				
				260	37·6						

Experimental

Alumina used for chromatography was supplied by Peter Spence & Sons, Ltd., as Activated Alumina Type H, 100/200 Mesh.

Preparation of Oxindoles.—The improved general method employed is exemplified by the preparation of oxindole. ω-Chloroacetanilide (10 g.) was added to a fused mixture of anhydrous aluminium chloride (50 g.) and sodium chloride (10 g.) at 140° and the temperature was raised rapidly to 220°. Brisk effervescence with evolution of hydrogen chloride took place. The melt was kept at 220—230° for 2 min. and then allowed to cool. The product was decomposed with crushed ice and a little dilute hydrochloric acid. Oxindole separated in an almost colourless crystalline form. It was collected, washed with a small volume of cold water, and recrystallised from water (with charcoal). Oxindole (5 g.) separated in colourless needles, m. p. 126—127°. The optimum temperature for the reaction, which varies with different chloroacetanilides, is recognised by brisk effervescence with evolution of hydrogen chloride.

Naphth[3 : 2 : 1-cd]*oxindole.*—A solution of 3-*o*-aminobenzylideneoxindole (1·5 g.), prepared by the method of Borsche, Wagner-Roemmich, and Barthenheier (*loc. cit.*), in concentrated sulphuric acid (6 c.c.), was diluted with water (50 c.c.), and the resultant suspension was stirred and diazotised at 0° by slow addition of 5N-sodium nitrite (5 c.c.). After 1½ hours' stirring at 0° the mixture was diluted with water (150 c.c.) and filtered, and the residue washed with water. Urea (0·5 g.) was added to the combined filtrates, and freshly prepared copper powder (cf. Gattermann, *Ber.*, 1890, **23**, 1219) (1·5 g.) was added to the solution stirred at room temperature. Nitrogen was evolved and stirring was continued for 48 hr. to complete the reaction. The mixture was extracted with chloroform and then with ether, and the combined extracts were dried ($MgSO_4$) and evaporated. The residual solid (1 g.) was passed in alcohol–ether (1 : 2 v/v) through a column of alumina (40 g.). Elution with the same solvent gave naphth[3 : 2 : 1-*cd*]oxindole (0·4 g.) in prisms, m. p. 229°, from alcohol (Found: C, 81·9; H, 4·1. Calc. for $C_{15}H_9ON$: C, 82·1; H, 4·1%). Further elution with alcohol gave a brown tar (0·6 g.). Pschorr and Popovici (*loc. cit.*) record m. p. 230° for this compound prepared from *o*-nitro-α-*o'*-nitrophenylcinnamic acid.

7-*Methyloxindole.*—7-Methyloxindole was prepared from ω-chloroacet-*o*-toluidide by the general method outlined above and also by the method of Stollé *et al.* (*J. pr. Chem.*, 1930, **128**, 4), modified by the use of double the quantity of aluminium chloride, but repeated crystallisation from benzene and purification by adsorption on silica gel gave needles, m. p. 175—182° (Found: C, 73·5; H, 6·1; N, 9·55. Calc. for C_9H_9ON: C, 73·4; H, 6·2; N, 9·5%). The benzylidene derivative had m. p. 224—225° (Found: C, 81·3; H, 5·6. Calc. for $C_{16}H_{13}ON$: C, 81·7;

H, 5·5%). Stollé records m. p. 200° for 7-methyloxindole, and Wahl and Faivret (*Ann. Chim.*, 1926, **5**, 349) m. p. 204° for 7-methyloxindole and m. p. 224° for the benzylidene derivative.

3-*Methylnaphth*[3 : 2 : 1-cd]*oxindole*.—A mixture of 7-methyloxindole (1·75 g.) and *o*-nitrobenzaldehyde (1·85 g.) was heated to 130° in an oil-bath and kept at this temperature until evolution of water vapour ceased. The cooled product was extracted with boiling glacial acetic acid and filtered. On cooling, 7-*methyl*-3-o-*nitrobenzylideneoxindole* (1·8 g.) separated, which crystallised from the same solvent (charcoal) in orange globules, m. p. 232° (Found: C, 68·0; H, 4·3. $C_{16}H_{12}O_3N_2$ requires C, 68·5; H, 4·7%). The nitro-compound (1 g.) was dissolved in the stannous chloride reagent (10 c.c.) (prepared from 9 g. of $SnCl_2,2H_2O$ in 15 c.c. of glacial acetic acid, saturated with hydrogen chloride and made up to 20 c.c. with the same solvent; Thiele and Dimroth, *Annalen*, **1899**, **305**, 114) by warming and then set aside overnight. The stannic chloride complex was decomposed with concentrated aqueous sodium hydroxide, the temperature being kept below 40°. The yellow solid was collected, washed well with dilute aqueous sodium hydroxide and with water, and then dried. Recrystallisation from methanol gave 3-o-*aminobenzylidene*-7-*methyloxindole* (0·6 g.) in golden-yellow needles, m. p. 222—223° (Found: C, 76·5; H, 5·6. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6%). The same compound was also obtained but in lower yield by the condensation of *o*-aminobenzaldehyde with 7-methyloxindole in alcohol containing a few drops of piperidine. 3-*o*-Aminobenzylidene-7-methyloxindole (1·5 g.) was diazotised and the resulting diazonium salt was decomposed with copper powder as described in the previous example. The product was isolated as before, but the alumina column was first eluted with benzene. Evaporation of the benzene solution left a white crystalline residue (0·15 g.), which on recrystallisation from light petroleum (b. p. 40—60°) gave 7-*methylbenzopyrano*[2 : 3-b]*indolenine* in rosettes of needles, m. p. 143—144° (Found: C, 82·6; H, 4·5; N, 6·15; *M*, 221. $C_{16}H_{11}ON$ requires C, 82·4; H, 4·85; N, 6·0%; *M*, 233). Subsequent elution with alcohol–ether (1 : 2) gave 3-*methylnaphth*[3 : 2 : 1-cd]*oxindole* (0·4 g.), which crystallised from benzene in yellow needles, m. p. 275—276° (Found: C, 82·7; H, 4·7. $C_{16}H_{11}ON$ requires C, 82·4; H, 4·85%). When precautions were not taken to minimise the rise in temperature during the preparation of the solution of the amine salt for diazotisation, the benzopyranoindolenine became the main product.

Derivatives of 5 : 7-*Dibromo-oxindole*.—This compound, m. p. 260°, was prepared by the bromination of oxindole as described by Sumpter, Miller, and Hendrick (*J. Amer. Chem. Soc.*, 1945, **67**, 1657). When boiled under reflux with two drops of piperidine, 5 : 7-dibromo-oxindole (1 g.) and benzaldehyde (1 c.c.) gave the 3-*benzylidene* derivative (0·8 g.) in yellow needles, m. p. 223—225° (from alcohol) (Found: C, 47·7; H, 2·6. $C_{15}H_9ONBr_2$ requires C, 47·5; H, 2·4%). In the same manner 5 : 7-*dibromo*-3-o-*nitrobenzylideneoxindole* (1·3 g.) was obtained from the dibromo-oxindole (1 g.) and *o*-nitrobenzaldehyde (0·75 g.) and crystallised from glacial acetic acid in orange needles, m. p. 257·5° (Found: C, 42·4; H, 1·9. $C_{15}H_8O_3N_2Br_2$ requires C, 42·45; H, 1·9%). Reduction of the nitro-compound (1 g.) with the stannous chloride reagent (10 c.c.) as described above gave 3-o-*aminobenzylidene*-5 : 7-*dibromo-oxindole* (0·91 g.), which crystallised from glacial acetic acid in needles, m. p. 251—252° (Found: Br, 40·5. $C_{15}H_{10}ON_2Br_2$ requires Br, 40·6%).

Decomposition of the Diazonium Sulphate prepared from 3-o-*Aminobenzylidene*-5 : 7-*dibromo-oxindole*.—(i) A cooled solution of the oxindole (1 g.) in concentrated sulphuric acid (6 c.c.) was diluted with water (25 c.c.) and diazotised at 0—5° with a solution of sodium nitrite (1·5 g.) in water (5 c.c.). After 1 hr. the mixture was diluted with water (150 c.c.) and filtered, the residue being washed with water. After the addition of urea (1 g.) to the combined filtrates, the red solution was boiled under reflux for 1 hr. The yellow precipitate (0·69 g.) separated from nitrobenzene and gave 7-*bromo*-3-o-*hydroxybenzylideneoxindole*, m. p. 248—250° (Found: C, 57·5; H, 3·0; Br, 25·6. $C_{15}H_{10}O_2NBr$ requires C, 57·0; H, 3·2; Br, 25·3%).

(ii) The diazonium sulphate was prepared from the base (1·5 g.) as described under (i). After the addition of urea to the filtered diazonium solution, copper powder (1·6 g.) was slowly added to the vigorously stirred solution at room temperature. After 44 hr. evolution of nitrogen had ceased and the precipitated solid was extracted with chloroform (3 × 250 c.c.) and then with ether (2 × 150 c.c.). The combined extracts were dried ($MgSO_4$) and evaporated to 50 c.c., which solution was passed down a column of alumina (70 g.; 6½″ × 1″). Elution with benzene gave an oil (0·02 g.) and then with alcohol gave a yellow solid, which was readsorbed on alumina and eluted with benzene. The resulting yellow solid (0·11 g.) gave 7-bromo-3-*o*-hydroxybenzylideneoxindole, m. p. 248—250°, as in method (i), but subsequent elution with ether gave 3-*bromonaphth*[3 : 2 : 1-cd]*oxindole* (0·2 g.), m. p. 185—186°, from ether (Found: Br, 27·3. $C_{15}H_8ONBr$ requires Br, 26·85%).

Derivatives of 5-*Bromo-oxindole*.—5-Bromo-oxindole (0·5 g.), prepared by the method of Sumpter, Miller, and Hendrick (*loc. cit.*), and benzaldehyde (0·25 c.c.) heated at 135° gave 3-*benzylidene*-5-*bromo-oxindole* (0·4 g.) in yellow needles, m. p. 197—199°, from ethanol (Found: Br, 26·2. $C_{15}H_{10}ONBr$ requires Br, 26·6%). In similar manner, 5-bromo-oxindole (1 g.) and *o*-nitrobenzaldehyde (0·75 g.) gave 5-*bromo*-3-*o*-*nitrobenzylideneoxindole* (1·45 g.) in red-orange clusters, m. p. 228—230°, from glacial acetic acid (Found: Br, 22·4. $C_{15}H_9O_3N_2Br$ requires Br, 23·2%). Reduction of the nitro-compound (1 g.) with the stannous chloride reagent (10 c.c.), as described above, gave 3-*o*-*aminobenzylidene*-5-*bromo-oxindole* (0·55 g.) in yellow crystals from methanol, which partially melted at 205° and finally at 310—320°, probably owing to the formation of a high-melting quinindoline derivative (Found: Br, 25·0. $C_{15}H_{11}ON_2Br$ requires Br, 25·4%).

1-*Bromonaphth*[3 : 2 : 1-cd]*oxindole*.—A fine suspension of 3-*o*-aminobenzylidene-5-bromo-oxindole (1·5 g.) in a mixture of concentrated hydrochloric acid (15 c.c.) and water (30 c.c.) was diazotised at 0—5° with sodium nitrite (2 g.) in water (10 c.c.). After 1 hr. water (150 c.c.) was added, and the solution filtered, the residue being washed with water. Urea (1 g.) was added to the combined filtrates, followed by copper powder (1·5 g.). Nitrogen was immediately evolved, and after being kept overnight the suspension was extracted with chloroform (2 × 250 c.c.) and then with ether (2 × 150 c.c.). The combined dried ($MgSO_4$) extracts were concentrated to about 50 c.c. and passed through an alumina column (70 g.). Elution with ether gave first an orange-coloured oil (0·16 g.) and then 1-*bromonaphth*[3 : 2 : 1-cd]*oxindole* (0·4 g.), which crystallised from benzene in pale yellow needles, m. p. 278—279° (Found: C, 60·7; H, 2·9. $C_{15}H_8ONBr$ requires C, 60·4; H, 2·7%).

Derivatives of 3-*Veratrylideneoxindole*.—Oxindole (1·3 g.) and veratraldehyde (1·66 g.) heated at 125° gave in almost quantitative yield 3-*veratrylideneoxindole*, which separated from acetone in golden-yellow needles, m. p. 212·5—213·5° (Found: C, 72·6; H, 5·5; N, 5·05. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·0%). In similar manner, oxindole (1·47 g.) and 6-nitroveratraldehyde (2·11 g.), heated at 130—140° with the addition of one drop of piperidine, gave 3-6′-*nitroveratrylideneoxindole* (3·0 g.), which separated from glacial acetic acid in orange-red needles, which sintered at 222° and finally melted at 235—236° (Found: C, 62·15; H, 4·6; N, 8·05. $C_{17}H_{14}O_5N_2$ requires C, 62·6; H, 4·3; N, 8·6%). Borsche, Wagner-Roemmich, and Barthenheier (*Annalen*, 1942, **550**, 172) reported m. p. 261° for this compound. Reduction of the nitro-compound (0·35 g.) with the stannous chloride reagent (5 c.c.), as described in the previous examples, gave 3-6′-*aminoveratrylideneoxindole* (0·3 g.), which separated from methanol in orange-red plates, m. p. 213—214° on rapid heating (Found: C, 68·5; H, 5·6; N, 8·9. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%). When slowly heated the amine partially melted at 214°, resolidified, and finally melted at 261—264°. Borsche, Wagner-Roemmich, and Barthenheier (*loc. cit.*) were unable to purify this compound and record m. p. 110—115° for the crude product.

8 : 9-*Dimethoxynaphth*[3 : 2 : 1-cd]*oxindole*.—A suspension of 3-6′-aminoveratrylideneoxindole (1·5 g.) in a mixture of concentrated sulphuric acid (8·25 c.c.) and water (25 c.c.) was diazotised at 0—5° with sodium nitrite (2 g.) in water (5 c.c.). After 1 hr. at 0° the suspension was diluted with water (150 c.c.) and filtered, and the residue (0·4 g.) washed with water. Urea (1 g.) was added to the filtrate, which was then stirred for 24 hr. at room temperature after the addition of copper powder (1·5 g.), a further quantity (1 g.) being added after 15 hr. The product was extracted with chloroform and ether, and the extracts were concentrated and passed through alumina as in previous examples. Benzene eluted a yellow oil (0·05 g.), after which benzene–ether (1 : 2 by vol.) eluted cis-3-*veratrylideneoxindole* (0·14 g.), m. p. 161—162°, in orange-yellow crystals from light petroleum (b. p. 40—60°) (Found: C, 72·3; H, 4·9; N, 4·5. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·3; N, 5·0%). Recrystallisation from acetone gave *trans*-3-veratrylideneoxindole in yellow plates, m. p. 210—211°, undepressed on admixture with the product from the action of veratraldehyde on oxindole. Further elution of the column with alcohol gave 8 : 9-*dimethoxynaphth*[3 : 2 : 1-cd]*oxindole* (0·6 g.), which separated from methanol in pale yellow micro-crystals which melted partially at 278° and finally at 296—297° (Found: C, 72·7; H, 4·7. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%).

Derivatives of 3-*Piperonylideneoxindole*.—Oxindole (1 g.) and piperonaldehyde (1·05 g.) at 125—130° gave in quantitative yield 3-*piperonylideneoxindole*, which separated from alcohol in yellow needles, m. p. 210—211° (Found: C, 72·2; H, 3·8. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·15%). In similar manner oxindole (0·67 g.) and 6-nitropiperonaldehyde at 125—130°, with a drop of piperidine, gave 3-6′-*nitropiperonylideneoxindole* (1·23 g.) in orange needles from glacial acetic acid which darkened at 245° and partially melted at 254° (Found: C, 61·85; H,

3·6. $C_{16}H_{10}O_5N_2$ requires C, 61·9; H, 3·2%). Reduction of the nitro-compound (1 g.) with the stannous chloride reagent (10 c.c.) (p. 1700) gave 3-6′-aminopiperonylideneoxindole (0·9 g.) in orange-red needles from alcohol, which melted partially at 226°, as recorded by Armit and Robinson (*J.*, 1925, **127**, 1612), who obtained it from oxindole and 6-aminopiperonaldehyde.

8 : 9-*Methylenedioxynaphth*[3 : 2 : 1-cd]*oxindole*.—A suspension of 3-6′-aminopiperonylideneoxindole (1·5 g.) in a mixture of concentrated hydrochloric acid (12 c.c.) and water (30 c.c.) was diazotised at 0° with sodium nitrite (1·75 g.) in water (10 c.c.). The resulting diazonium chloride, after the addition of urea (1 g.), was decomposed with copper powder, and the product worked up as in the preceding examples. Elution with benzene gave a yellow oil (0·03 g.), after which elution with ether gave 8 : 9-*methylenedioxynaphth*[3 : 2 : 1-cd]*oxindole* (0·67 g.), which separated from ethanol in yellow plates which darkened at 280° and melted at 298—300° (decomp.) (Found: C, 72·4; H, 3·4; N, 5·4. $C_{16}H_9O_3N$ requires C, 73·0; H, 3·4; N, 5·3%).

Derivatives of 3-m-*Chlorobenzylideneoxindole*.—Oxindole (0·5 g.) and *m*-chlorobenzaldehyde (0·5 g.) at 130° gave 3-m-*chlorobenzylideneoxindole* (0·3 g.) after purification by adsorption on alumina. It separated from benzene–light petroleum (b. p. 40—60°) in yellow needles, m. p. 164° (Found: C, 70·8; H, 4·1. $C_{15}H_{10}ONCl$ requires C, 70·5; H, 3·9%). In similar manner oxindole (0·67 g.) and 5-chloro-2-nitrobenzaldehyde (0·92 g.), prepared by the method of Alford and Schofield (*J.*, 1952, 2105), at 110—115°, gave 3-(5-*chloro*-2-*nitrobenzylidene*)*oxindole* (1·5 g.) in orange needles from glacial acetic acid, m. p. 247—248° (Found: Cl, 12·0. $C_{15}H_9O_3N_2Cl$ requires Cl, 11·8%). Reduction of the nitro-compound (1 g.) with the stannous chloride reagent (12 c.c.) (see above) gave 3-(2-*amino*-5-*chlorobenzylidene*)*oxindole* (0·85 g.), which separated from methanol in yellow needles, m. p. 218—219° after sintering at 211° (Found: C, 66·3; H, 4·1. $C_{15}H_{11}ON_2Cl$ requires C, 66·55; H, 4·1%).

8-*Chloronaphth*[3 : 2 : 1-cd]*oxindole*.—A suspension of 3-(2-amino-5-chlorobenzylidene)-oxindole (1·5 g.) in concentrated hydrochloric acid (13 c.c.) and water (30 c.c.) was diazotised at 0—5° with sodium nitrite (1·7 g.) in water (10 c.c.), the diazonium solution was decomposed with copper powder (1·5 g.), and the product worked up as in the preceding examples. Elution with ether gave 8-*chloronaphth*[3 : 2 : 1-cd]*oxindole* (1·2 g.), which separated from alcohol in pale yellow needles which darkened at 285—286° and finally melted at 305—306° (decomp.) (Found: C, 70·5; H, 3·3; Cl, 13·7. $C_{15}H_8ONCl$ requires C, 71·0; H, 3·2; Cl, 14·0%).

Derivatives of N-*Phenyloxindole*.—*N*-Phenyloxindole (2 g.; m. p. 121·5°), prepared by the general method above, and *o*-nitrobenzaldehyde (1·5 g.) with one drop of piperidine at 125—130° gave 3-*o*-*nitrobenzylidene*-N-*phenyloxindole* (2·1 g.) in orange needles, m. p. 215—216°, from glacial acetic acid (Found: C, 73·3; H, 3·8. $C_{21}H_{14}O_3N_2$ requires C, 73·7; H, 4·1%). Reduction of the nitro-compound (4 g.) by the method described in previous examples gave 3-*o*-aminobenzylidene-*N*-phenyloxindole, m. p. 125—130°, in almost quantitative yield, probably as a mixture of geometrical isomerides. Recrystallisation from methanol gave the cis-*isomeride* (2·1 g.) in hard needles, m. p. 161° (Found: C, 81·0; H, 5·2; N, 8·7. $C_{21}H_{16}ON_2$ requires C, 80·7; H, 5·1; N, 9·0%).

4-*Phenylnaphth*[3 : 2 : 1-cd]*oxindole*.—Diazotisation of 3-*o*-aminobenzylidene-*N*-phenyloxindole (2·1 g.) in dilute hydrochloric acid and subsequent decomposition with copper powder gave a yellow solid which was extracted with chloroform (2 × 150 c.c.); the extract was dried ($MgSO_4$), diluted with benzene (30 c.c.), and concentrated to about 50 c.c. Chromatographic adsorption on alumina (70 g.) and elution with benzene gave 4-*phenylnaphth*[3 : 2 : 1-cd]-*oxindole* (0·56 g.) in pale yellow needles, m. p. 178—179°, from alcohol (Found: C, 85·35; H, 4·5. $C_{21}H_{13}ON$ requires C, 85·4; H, 4·4%).

3-α-*Picolinylideneoxindole*.—A mixture of isatin (7 g.), α-picoline (10 c.c.), and fused zinc chloride (8 g.) was heated under reflux for 1 hr. and then poured into ice-water. The dark product was dissolved in glacial acetic acid, the solution filtered, and the product precipitated with ammonia, the whole operation being repeated a second time. After being washed well with water and dried *in vacuo*, 3-α-*picolinylideneoxindole* (6 g.) was obtained as a brick-red amorphous powder, m. p. 154—155° after sintering at 110°, which was only sparingly soluble in most organic solvents and could not be recrystallised (Found: N, 12·5. $C_{14}H_{10}ON_2$ requires N, 12·6%).

3-*Quinaldinylideneoxindole*.—(*a*) Quinaldine (7·15 g.), isatin (7·35 g.), and fused zinc chloride (8 g.) were heated at 170° (air-condenser). When the vigorous reaction had subsided the dark red mass was extracted first with boiling water and then with boiling alcohol. Recrystallisation of the residue from benzene gave 3-*quinaldinylideneoxindole* (4 g.) in yellow needles, m. p. 229—230° (Found: C, 79·3; H, 4·4. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). (*b*) A solution of quinoline-2-aldehyde (0·78 g.) (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2655) and oxindole

(0·67 g.) in alcohol (5 c.c.) containing one drop of piperidine was boiled under reflux for 30 min. The orange-yellow product which separated was collected, washed with a little cold alcohol, and recrystallised from benzene. 3-Quinaldinylideneoxindole (1·1 g.) was obtained in yellow needles, m. p. 225—266°, undepressed on admixture with the product prepared by method (*a*) above.

3-4′-*Hydroxyquinaldinylideneoxindole*.—A mixture of isatin (7·4 g.), 4-hydroxyquinaldine (7·95 g.), fused sodium acetate (10 g.), glacial acetic acid (50 c.c.), acetic anhydride (2 c.c.), and fused zinc chloride (8 g.) was boiled under reflux for 5 hr. The dark solution was poured into water, and the precipitate collected. A further precipitate was obtained on addition of ammonia to the filtrate. The combined solid product (2 g.) proved to be very sparingly soluble in most organic solvents, but recrystallisation from a large volume of methyl alcohol gave 3-4′-*hydroxyquinaldinylideneoxindole* as a fluffy yellow solid, m. p. above 300° (Found: C, 74·6; H, 4·2. $C_{18}H_{12}O_2N_2$ requires C, 75·0; H, 4·2%).

3-*Nitroquinaldine*.—A solution of toluene-*p*-sulphonhydrazide (3·7 g.) (Albert and Royer, *J.*, 1949, 1150) in warm chloroform (100 c.c.) was added to a solution of 4-chloro-3-nitroquinaldine (4·4 g.) (Adams and Hey, *J.*, 1951, 1526) in chloroform (50 c.c.). After this had stood for 6 days, dry hydrogen chloride was passed into the suspension for 10 sec., and it was then left overnight. The 3-*nitro*-4-*toluene*-p-*sulphonhydrazinoquinaldine hydrochloride* which separated in almost quantitative yield was collected and washed with a small volume of cold chloroform. A sample recrystallised from 95% ethyl alcohol by partial evaporation in a current of air to avoid decomposition was obtained in yellow translucent crystals, m. p. 176—178° (Found: C, 49·6; H, 5·3. $C_{17}H_{16}O_4N_4S,HCl$ requires C, 49·9; H, 5·2%). The hydrochloride (20 g.) was added slowly to sodium carbonate (40 g., anhyd.) in water (400 c.c.) at 65°. The mixture, which became purple as the solid decomposed with evolution of nitrogen, was heated under reflux on a boiling-water bath for 15 min. and then boiled for 100 min. Steam-distillation of the resulting mixture gave 3-*nitroquinaldine* (1·1 g.) in colourless needles, m. p. 110—111° (Found: C, 63·8; H, 4·6. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·25%).

3-3′-*Nitroquinaldinylideneoxindole*.—3-Nitroquinaldine (1 g.), isatin (0·8 g.), and fused sodium acetate (1 g.) in acetic anhydride (0·2 c.c.) and glacial acetic acid (6 c.c.) were boiled under reflux for 5 hr. When cold, 3-3′-*nitroquinaldinylideneoxindole* (0·5 g.) separated; it crystallised from glacial acetic acid in brick-red needles, m. p. 235—236° (Found: C, 68·1; H, 3·5. $C_{18}H_{11}O_3N_3$ requires C, 68·1; H, 3·5%).

3-o-*Nitrobenzylidenethio-oxindole*.—(*a*) A mixture of thio-oxindole (0·37 g.), prepared as described by Glauert and Mann (*loc. cit.*), and *o*-nitrobenzaldehyde (0·37 g.) was heated to 130° with one drop of piperidine. After 20 min. the oil was triturated with alcohol, and the solid product was collected, washed with cold alcohol and ether, and recrystallised from glacial acetic acid. 3-o-*Nitrobenzylidenethio-oxindole* (0·56 g.) was obtained in mustard-yellow needles, m. p. 147° (Found: C, 63·2; H, 2·8; N, 4·7. $C_{15}H_9O_3NS$ requires C, 63·4; H, 3·2; N, 4·95%). (*b*) The same product was obtained when a solution of thio-oxindole (1 g.) and *o*-nitrobenzaldehyde (1 g.) in ethyl alcohol (5 c.c.) was boiled under reflux for 10 min. with two drops of piperidine. The product (1·6 g.) separated in a pure crystalline form.

Reduction of 3-o-*Nitrobenzylidenethio-oxindole*.—Reduction of the nitro-compound (1 g.) with the stannous chloride reagent (10 c.c.), as described above for the nitrobenzylideneoxindoles gave, on decomposition of the stannichloride complex, 3-o-*mercaptophenylcarbostyril* (0·7 g.), which separated from ethyl alcohol in needles, m. p. 200—201° (Found: C, 70·6; H, 4·5; N, 5·9. $C_{15}H_{13}ONS$ requires C, 71·1; H, 4·35; N, 5·5%). The same product (1·22 g.; m. p. 200—201°) was obtained on heating under reflux for 45 min. thio-oxindole (1·5 g.) and *o*-aminobenzaldehyde (1·2 g.) in ethyl alcohol (7 c.c.) containing two drops of piperidine. Refluxing of an alcoholic solution of 2 : 4-dinitrochlorobenzene and the thiol in alcoholic sodium hydroxide gave the 2 : 4-*dinitrophenylthio*-derivative, which crystallised from dioxan in greenish-yellow needles, m. p. 227—228° (Found: C, 59·8; H, 3·3. $C_{21}H_{13}O_5N_3S$ requires C, 60·1; H, 3·1%).

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Studies with Acetylenes. Part I. Some Reactions of Grignard Reagents with Alk-1-ynyl and Alk-1-enyl Halides.

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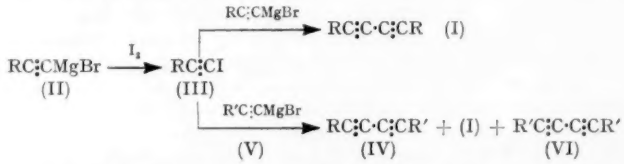
In the presence of small amounts of cuprous or cobaltous chloride, alk-1-ynyl halides condense with alkyl, aryl, and alkynyl Grignard reagents to give disubstituted acetylenes or diacetylenes. In the absence of the metal chlorides, alk-1-ynyl halides and alkyl (or aryl) Grignard reagents undergo metathesis.

With a cobaltous chloride catalyst, alkynyl Grignard reagents will also react with alk-1-enyl and alkyl halides giving vinylacetylenes and alkyl-substituted acetylenes, respectively.

This communication describes some reactions of alkynyl Grignard reagents with alk-1-ynyl and alk-1-enyl halides, and of alkyl and aryl Grignard reagents with alk-1-ynyl halides. These reactions, if carried out in the presence of cuprous or cobaltous chloride, afford diacetylenes, vinylacetylenes, and disubstituted acetylenes.

Alkynyl Grignard Reagents.—Grignard and his collaborators (Grignard and Perrichon, *Ann. Chim.*, 1926, **5**, 13; Grignard and Tchéoufaki, *Compt. rend.*, 1929, **188**, 357) reported that diacetylenes (I) were formed in good yield on treatment of an alkynylmagnesium halide (II) with half the amount of iodine required to give the alkynyl iodide (III). Although it was also stated that unsymmetrically substituted diacetylenes (IV) could be obtained by reaction of the alkynyl iodide (III) with the bromomagnesio-derivative (V) of the appropriate acetylene, the only example quoted was the preparation of "phenyltriacetylene" from phenylethynylmagnesium bromide and "iododiacetylene." However, this result must now be discounted since Schlubach and Franzen (*Annalen*, 1951, **573**, 115) have shown that iododiacetylene has properties very different from those reported by Grignard and Tchéoufaki for their starting material.



In connection with a study of methods for the synthesis of erythrogenic acid and related compounds (cf. Black and Weedon, *J.*, 1953, 1785), Grignard's route to diacetylenes has been re-examined. Treatment of hexynylmagnesium bromide with 0·5 mol. of iodine, following Grignard's procedure, gave mainly iodohexyne (III; R = Bu), and only very small amounts of dodecadiyne (I; R = Bu). This failure of the iodohexyne to react further with the excess of Grignard reagent was reminiscent of the difficulty encountered by Danehy, Killian, and Nieuwland (*J. Amer. Chem. Soc.*, 1936, **58**, 611) in repeating Grignard and Lapayre's (*Bull. Soc. chim.*, 1928, **43**, 141) condensation of alkynylmagnesium halides with allyl bromide. The American authors found small amounts of cuprous chloride very effective in promoting the desired condensation. When this catalyst was used in the reaction of hexynylmagnesium bromide with iodine, dodecadiyne was formed in the same yield (70%) as that obtained by Grignard and Tchéoufaki without addition of catalyst.

Less satisfactory results were achieved in the preparation of unsymmetrical diacetylenes, owing to the intrusion of side reactions not mentioned by Grignard and his co-workers. Treatment of iodohexyne (III; R = Bu) with phenyl- or *cyclo*hex-1-enyl-ethynylmagnesium bromide in the presence of cuprous chloride gave mixtures containing three diacetylenes (I, IV, and VI; R = Bu, R' = Ph or *cyclo*hexenyl), from which the required unsymmetrical products were separated in only *ca.* 35% yield. A similar condensation of 1-bromohex-1-

yne with phenylethynylmagnesium bromide yielded a mixture from which phenyloctadiyne (IV; R = Bu, R′ = Ph) was isolated (15%), but a single attempt to prepare the latter from 1-bromo-2-phenylacetylene and hexynylmagnesium bromide was, surprisingly, unsuccessful.

Since Kharasch and his collaborators have shown that small amounts of cobaltous chloride exert a strong influence on the course of many reactions with alkyl and aryl Grignard reagents (cf. Hey, *Ann. Reports*, 1944, **41**, 195; 1948, **45**, 160), the use of this catalyst was considered. Condensation of hexynylmagnesium bromide with 1-bromohex-1-yne and with 1-bromo-2-phenylacetylene in presence of cobaltous chloride gave (30%) dodecadiyne and phenyloctadiyne, respectively. Similarly, reaction of phenylethynylmagnesium bromide with 1-bromo-2-phenylacetylene gave (30%) diphenylbutadiyne (I; R = Ph), but an attempt to prepare phenyloctadiyne from hexynylmagnesium bromide and 1-iodo-2-phenylacetylene failed, diphenylbutadiyne being the only diacetylene isolated (28%). Recently Schlubach and Franzen (*Annalen*, 1951, **572**, 116), using the same catalyst, prepared diphenylbutadiyne (I = Ph) in 75% yield from iodophenylacetylene and phenylethynylmagnesium bromide, but were unable to effect an analogous reaction between the same Grignard reagent and di-iodoacetylene.

The simultaneous formation of symmetrical diacetylenes as by-products during the preparation of unsymmetrical compounds is probably due to the initial establishment of an equilibrium of the following type :

$$RC{:}CI + R'C{:}CMgBr \rightleftharpoons RC{:}CMgBr + R'C{:}CI$$

[Analogous interchange reactions have been observed with alkyl and aryl Grignard reagents in the absence of catalyst (see below); also in the reaction of alkyl and aryl Grignard reagents with organic halides in the presence of cobaltous chloride (Kharasch and Fuchs, *J. Org. Chem.*, 1945, **10**, 292).] Subsequent condensation would then lead to a mixture of three diacetylenes, as is observed.

The majority of the results described above are summarised in Table 1. Clearly the alkynyl iodides are much superior to the bromides for the preparation of the symmetrical

TABLE 1. *Yield* (%) *of diacetylene* (RC:C·C:CR′). [The use of a cuprous or cobaltous chloride catalyst is indicated by (Cu) or (Co), respectively.]

Grignard reagent (R′C:CMgBr)	Halide: BuC:CI	BuC:CBr	PhC:CI	PhC:CBr
BuC:CMgBr	<10; 71 * (Cu)	28(Co)	0(Co)	0(Cu); 31(Co)
PhC:CMgBr	35(Cu)	15(Cu)	75(Co) †	39(Co)
—C:CMgBr	34(Cu)			

* Iodohexyne formed *in situ*. † Schlubach and Franzen, *Annalen*, 1951, **572**, 116.

diacetylenes. The low yields (≯35%) of unsymmetrical diacetylenes from the alkynyl iodides may be attributed mainly to interchange reactions of the type discussed above leading to symmetrical products, but there is some evidence that the alkynyl bromides are less reactive in these reactions as well as in the condensations with alkynyl Grignard reagents.

Since aryl and alkyl Grignard reagents condense with alk-1-enyl halides in presence of cobaltous chloride (Kharasch and Fuchs, *J. Amer. Chem. Soc.*, 1943, **65**, 504), it seemed probable that in the above reactions the alk-1-ynyl halides might be replaced by alk-1-enyl halides, thus providing a new route to vinylacetylenes. The catalysed condensations of hexynylmagnesium bromide with *iso*butenyl bromide, and of phenylethynylmagnesium bromide with styryl bromide, gave the vinylacetylenes, $CMe_2{:}CH{\cdot}C{:}CBu$ and PhCH:CH·C:CPh, respectively. The recent claim (Herbert, *Chem. Ber.*, 1952, **85**, 475) that vinyldiacetylene can be obtained by heating vinyl bromide and monosodiodiacetylene in an inert solvent is of interest in connection with these results.

Both aryl and alkynyl Grignard reagents undergo coupling reactions on treatment with 1 mol. of cupric halide, giving symmetrical diaryls (Krizewsky and Turner, *J.*, 1919,

559; Sakellarios and Kyrimis, *Ber.*, 1924, **57**, 322) and diacetylenes (Danehy and Nieuwland, *J. Amer. Chem. Soc.*, 1936, **58**, 1609), respectively. The production of diaryls in good yield from the Grignard reagent and 1 mol. of an alkyl halide in the presence of cobaltous chloride (Kharasch *et al.*, *ibid.*, 1941, **63**, 2316; 1943, **65**, 493; 1944, **66**, 365) suggested that an analogous coupling reaction might be achieved with alkynyl Grignard reagents. However, all attempts to prepare diacetylenes in this way have been unsuccessful. Thus from hexynylmagnesium bromide and butyl bromide, in the presence of cobaltous chloride, the only product isolated was dec-5-yne. Condensations of this type between an alkyl halide and an alkynyl Grignard reagent have been reported to occur even without catalyst, but are exceptional (cf. Jacobs, *Org. Reactions*, 1949, **5**, 1).

Alkyl and Aryl Grignard Reagents.—Having examined the behaviour of alk-1-ynyl halides towards ethynyl Grignard reagents, we studied some analogous reactions with typical alkyl and aryl Grignard reagents. Such organometallic compounds have been condensed with dichloroacetylene (ClC:CCl) to give chloroacetylenes (R'C:CCl) (Ott and Bossaller, *Ber.*, 1943, **76**, 88). However, di-iodoacetylene, iododiacetylene, and various bromoacetylenes have been reported to undergo metathetical reactions:

$$RC{:}CBr + R'MgBr \longrightarrow RC{:}CMgBr + R'Br$$

(Jositsch, *Bull. Soc. chim.*, 1906, **36**, 177; Kharasch, Lambert, and Urry, *J. Org. Chem.*, 1945, **10**, 298; Moulin, *Helv. Chim. Acta*, 1951, **34**, 2416; Schlubach and Franzen, *Annalen*, 1951, **572**, 116; **573**, 115). The effect of catalyst is known only in the reaction of 1-bromo-2-phenylacetylene with methylmagnesium bromide: condensation, instead of the normal interchange, occurred in the presence of cobaltous chloride giving phenylpropyne in 62% yield (Kharasch, Lambert, and Urry, *loc. cit.*). The yield of phenylpropyne in our catalysed reaction was $\geqslant$40%, phenylacetylene (*ca.* 30%) being formed simultaneously by metathesis.

Similarly *n*-butylmagnesium bromide and either 1-bromo- or 1-iodo-2-phenylacetylene with cobaltous chloride gave phenylhexyne in 32—34% yield; by use of cuprous chloride the yield of phenylhexyne from 1-bromo-2-phenylacetylene was raised to 46%. Reaction of butylmagnesium bromide with 1-bromo-2-phenylacetylene in absence of catalyst gave both phenylacetylene and butyl bromide, in *ca.* 60% yield, by the normal interchange reaction. The same bromo-acetylene and phenylmagnesium bromide in presence of cobaltous chloride gave tolane (PhC:CPh) in 39% yield. While the method of alkylating an acetylene *via* a halogen derivative will not, in general, afford any advantage over existing standard procedures [*e.g.*, treatment of the sodium derivative with an alkyl halide (cf. Jacobs, *loc. cit.*)], a method has not previously been available for the replacement of an acetylenic hydrogen atom by an aryl group.

The structures of the various products mentioned above were readily confirmed by comparing their light-absorption properties with those reported for authentic specimens, or for compounds with similar chromophores (see Table 2).

Experimental

Light-absorption measurements were determined in alcohol, unless otherwise stated.

Intermediates.—1-Bromo-2-phenylacetylene was prepared from phenylacetylene and potassium hypobromite (Straus, Kollek, and Heyn, *Ber.*, 1930, **63**, 1868); it had b. p. 58—61°/1 mm., 42°/0·3 mm., n_D^{18} 1·6100—1·6120. Light absorption: see Table 2. [The di-iodide had m. p. 64° (Nef, *loc. cit.*, gives m. p. 65—66°).] 1-Bromohex-1-yne was prepared similarly from hexyne in 80% yield, and from hexynylmagnesium bromide and bromine in 50% yield (cf. McCusker and Vogt, *J. Amer. Chem. Soc.*, 1937, **59**, 1307); it had b. p. 40—41°/10 mm., n_D^{19} 1·4666. 1-Iodohex-1-yne was obtained by the action of iodine on hexynylsodium in liquid ammonia (cf. Vaughn and Nieuwland, *ibid.*, 1933, **55**, 2150), and on hexynylmagnesium bromide in ether (cf. Grignard and Perrichon, *loc. cit.*) in 90 and 70% yield, respectively; it had b. p. 85°/40 mm., n_D^{19} 1·5173. The halogenoacetylenes all decomposed slowly at 0°.

Preparation of Grignard Reagents.—Throughout most of the investigations, the following procedures were adopted. Ethereal solutions (*ca.* 1M) of alkyl and aryl Grignard reagents were prepared at 0°. To ensure complete removal of any excess of alkyl or aryl halide (traces were

found to have a deleterious effect on some of the subsequent condensations) the resulting solutions were boiled under reflux over magnesium (0·25 mol.) for 1·5 hr., and then cooled and decanted. Acetylenic Grignard reagents were prepared by heating an ethereal solution of ethylmagnesium bromide with the acetylene (1·1 mol.) under reflux for 1 hr. after the evolution of ethane ceased (total time *ca.* 3—4 hr.).

Condensations.—Unless otherwise stated the following general procedure was used.

Cobaltous chloride (dried at 150° *in vacuo*) or cuprous chloride was added to the stirred, well-cooled (ice–salt bath) ethereal solution of the Grignard reagent. The alkynyl or alkenyl halide was added during *ca.* 1·5 hr., and the mixture was stirred overnight at room temperature.

TABLE 2. *Light-absorption maxima, in mμ* (ε *in parentheses*).

BuC:C·C:CBu	227(560)	239(490)	249—255(360)			
,, [1]	228(440)	239(390)	254(240)			
PhC:C·C:CBu	245(7500)	257(19,000)	271(26,000)	288(23,000)		
PhC:C·C:CH [2]	243(6000)	255(13,500)	269(21,500)	284(18,500)		
C_6H_9·C:C·C:CBu [3]	—	239(6000)	245(4500)	251(12,500)	265(18,000)	282(14,500)
CHMe:CH·C:C·C:CH [1]	230(2250)	238(5000)	—	251(10,000)	264(14,000)	280(11,000)
PhC:C·C:CPh	227(29,000)	247(29,000)	257(25,000)	287(22,000)	306(30,500)	327(30,500)
,, [4]	—	—	—	287	304	326
C_6H_9·C:C·C:C·C_6H_9 [5]	229(37,500)	236(37,500)	246(27,500)	261(9000)	277(16,000)	292(22,000)
,,	—	237(34,000)	246(29,000)	260(8000)	275(16,000)	291(23,000)
C_6H_9·C:C·C:C·C_6H_9	—	—	—	—	—	308(17,000)
,, [5]	—	—	—	—	—	310(19,000)
CMe_2:CH·C:CBu	229(16,500)	235(13,500)				
CHMe:CH·C:CH [6]	222(11,000)	229 * (8000)				
PhCH:CH·C:CPh	308(35,000)	318(35,000)				
PhCH:CH·CH:CHPh [7]	—	328(41,000)				
PhC:CPh	281(26,500)	288(22,000)	297(26,500)			
,, [4]	278	288	296			
PhC:CH [8]	236(17,000)					
PhC:CMe	238(16,500)	249(16,500)				
PhC:CBu	240(18,000)	251(18,000)				
PhC:CBr	246(17,500)	251(17,500)				

[1] Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998. [2] Personal communication from Professor E. R. H. Jones and Dr. M. C. Whiting. [3] C_6H_9 = *cyclo*hex-1-enyl. [4] Schlubach and Franzen, *Annalen*, 1951, **573**, 110; determined in MeOH. [5] Bohlmann, *Chem. Ber.*, 1951, **84**, 545; determined in *cyclo*hexane; C_6H_9 = *cyclo*hex-1-enyl. [6] Armitage and Whiting, *J.*, 1952, 2005. [7] Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, *B*, **29**, 384. [8] Morton, Hassan, and Calloway, *J.*, 1934, 883; determined in hexane.

* Inflexion.

Excess of dilute acetic acid (10%) was added, and the ethereal layer was separated, washed with water, dried, and evaporated. The residue was then heated at 0·1 mm., and the low-boiling products were collected in a trap (alcohol–solid carbon dioxide) and subsequently distilled. High-boiling products were isolated by distillation of the tarry residue at 10^{-4} mm.

The specimens of unsymmetrical diacetylenes prepared from alkynyl iodides were frequently contaminated with traces of an iodine-containing impurity, which could be removed by treatment with alcoholic potassium hydroxide.

Yields of condensation products are based on the amount of organic halide used, allowance being made for the weight of recovered material where this is quoted.

Dodeca-5 : 7-diyne.—(*a*) Cuprous chloride was added to a stirred ethereal solution of hexynylmagnesium bromide (from 4·8 g. of magnesium and 16·5 g. of hexyne), and the mixture was boiled. A solution of iodine (25·5 g.) in ether (250 c.c.) was added rapidly, and heating under reflux was continued for 3 hr. The mixture was cooled and 2N-sulphuric acid was added. The ethereal layer was separated, washed with aqueous sodium thiosulphate (10% w/v), dried, and evaporated. Distillation of the residue gave dodeca-5 : 7-diyne (11·5 g.), b. p. 120°/13 mm., 85°/0·4 mm., n_D^{19} 1·4890 (Grignard and Tchéoufaki, *Compt. rend.*, 1929, **188**, 357, give b. p. 118—119°/4 mm.). Light absorption : see Table 2.

Without the copper chloride catalyst the yield of dodecadiyne did not exceed 10%, even after the reaction mixture had been heated for 9 hr.

(*b*) Reaction of hexynylmagnesium bromide (from 3·9 g. of magnesium and 13·2 g. of hexyne)

with 1-bromohex-1-yne (16·1 g.) in presence of cobaltous chloride (1·0 g.) gave dodeca-5 : 7-diyne (4·6 g.), b. p. 122°/10 mm., n_D^{19} 1·4890.

1-*Phenylocta*-1 : 3-*diyne*.—(*a*) Reaction of hexynylmagnesium bromide (from 3·9 g. of magnesium and 13·2 g. of hex-1-yne) with 1-bromo-2-phenylacetylene (18·2 g.) in presence of cobaltous chloride (1·0 g.) gave : (i) Recovered bromophenylacetylene (6·3 g., 35%). (ii) 1-*Phenylocta*-1 : 3-*diyne* (3·7 g.), b. p. 107°/1 mm., n_D^{23} 1·5922 (Found : C, 92·0; H, 7·65. $C_{14}H_{14}$ requires C, 92·25; H, 7·75%). Light absorption : see Table 2.

Repetition of the preceding experiment with cuprous chloride (0·6 g.) instead of cobaltous chloride led to the recovery of bromophenylacetylene (60%) and the formation of a tar; no diacetylenes were detected.

Reaction of hexynylmagnesium bromide with 1-iodo-2-phenylacetylene in presence of cobaltous chloride gave diphenylbutadiyne (28%), m. p. 85—86°, and iodohexyne (23%), but no phenyloctadiyne.

(*b*) To a boiling ethereal solution of phenylethynylmagnesium bromide (from 2·4 g. of magnesium and 11·0 g. of phenylacetylene) were added cuprous chloride (0·4 g.) and then, during 1 hr., 1-iodohex-1-yne (18·0 g.). The mixture was stirred and heated under reflux for 6 hr. and then cooled. 2N-Sulphuric acid was added, and the ethereal layer was separated, washed with aqueous sodium thiosulphate solution (10% w/v), dried, and evaporated. Distillation of the residue gave : (i) Crude dodeca-5 : 7-diyne (*ca.* 2 g.), b. p. 70—80°/0·4 mm. (ii) 1-Phenylocta-1 : 3-diyne (4—5 g.), b. p. 91—93°/0·01 mm., n_D^{19} 1·5942 (Found : C, 91·9; H, 8·05%). Light absorption : maxima, 2450, 2580, 2730, and 2900 Å; ε = 7500, 17,500, 29,000, and 24,500, respectively. (iii) Diphenylbutadiyne (3·2 g.), b. p. 100° (bath temp.)/10^{-5} mm., which crystallised from methanol in needles, m. p. 87°.

A similar condensation of phenylethynylmagnesium bromide with 1-bromohex-1-yne gave phenyloctadiyne in 15% yield.

1-cyclo*Hex*-1′-*enylocta*-1 : 3-*diyne*.—1-Iodohex-1-yne (20·0 g.) was added to a suspension of *cyclo*hex-1′-enylethynylmagnesium bromide (from 2·4 g. of magnesium and 10·6 g. of ethynyl-*cyclo*hexene) and cuprous chloride (0·4 g.) in ether (150 c.c.). The mixture was heated under reflux for 2 hr. and then cooled. 2N-Sulphuric acid was added and the products were isolated in the usual manner giving : (i) Dodeca-5 : 7-diyne (3·5 g.), b. p. 70—75° (mainly 72°)/0·3 mm., n_D^{22} 1·4891. (ii) 1-cyclo*Hex*-1′-*enylocta*-1 : 3-*diyne* (6·0 g.), b. p. 112°/0·2 mm., n_D^{22} 1·5537 (Found : C, 90·1; H, 9·8. $C_{14}H_{18}$ requires C, 90·25; H, 9·75%). Light absorption : see Table 2. (iii) A solid residue (4·0 g.) which, after sublimation at 80—90° (bath temp.)/10^{-5} mm. and crystallisation from methanol, gave 1 : 4-di*cyclo*hex-1′-enylbutadiyne as needles, m. p. and mixed m. p. 63° (Bohlmann, *Chem. Ber.*, 1951, **84**, 545, gives m. p. 60°). Light absorption : see Table 2.

The yield of *cyclo*hexenyloctadiyne was lowered to 26% when 0·25 mol. % instead of 2 mol.% of catalyst was used. In a reaction at 20° for 24 hr. appreciable quantities of material were recovered.

Diphenylbutadiyne.—Reaction of phenylethynylmagnesium bromide (from 3·9 g. of magnesium and 16·5 g. of phenylacetylene) with 1-bromo-2-phenylacetylene in presence of cobaltous chloride (1·0 g.) gave diphenylbutadiyne (7·0 g.), b. p. 110° (bath temp.)/10^{-5} mm. One crystallisation from alcohol gave needles, m. p. 86—87° (Grignard and Tchéoufaki, *Compt. rend.*, 1929, **188**, 357, give m. p. 86·5—87°). Light absorption : see Table 2.

2-*Methylnon*-2-*en*-4-*yne*.—Reaction of hexynylmagnesium bromide (from 3·9 g. of magnesium and 13·2 g. of hexyne) with *iso*butenyl bromide (13·5 g.) (Braude and Coles, *J.*, 1950, 2012) in presence of cobaltous chloride (1·0 g.) gave 2-*methylnon*-2-*en*-4-*yne* (3·2 g.), b. p. 100°/85 mm., n_D^{21} 1·4610 (Found : C, 88·0; H, 11·5%; hydrogen number, 48, equivalent to 2·8 double bonds. $C_{10}H_{16}$ requires C, 88·15; H, 11·85%). Light absorption : see Table 2.

1 : 4-*Diphenylbutenyne*.—Reaction of phenylethynylmagnesium bromide (from 3·9 g. of magnesium and 16·3 g. of phenylacetylene) with β-bromostyrene (18·3 g.) in presence of cobaltous chloride (1·0 g.) gave 1 : 4-diphenylbutenyne (5·0 g.), which crystallised from alcohol in needles, m. p. 95·5—96° [Pinckard, Wille, and Zechmeister, *J. Amer. Chem. Soc.*, 1948, **70**, 1938, give m. p. 96° (corr.)]. Light absorption : see Table 2. The m. p. of the product was strongly depressed on admixture with diphenylbutadiyne. Bromostyrene (9·3 g.) and phenylacetylene (3·3 g.) were recovered.

Dec-5-*yne*.—Reaction of butyl bromide (13·7 g.) with hexynylmagnesium bromide (from 3·9 g. of magnesium and 13·2 g. of hexyne) in presence of cobaltous chloride (1·0 g.) gave dec-5-yne (3·3 g.), b. p. 100°/80 mm., n_D^{22} 1·4340 (Bried and Hennion, *J. Amer. Chem. Soc.*, 1937, **59**, 1310, give b. p. 106°/80 mm., n_D^{25} 1·4311).

1-*Phenylprop*-1-*yne* (*cf. Kharasch, Lambert, and Urry*, J. Org. Chem., 1945, **10**, 298).—Reaction

of methylmagnesium bromide (from 3·9 g. of magnesium) and 1-bromo-2-phenylacetylene (18·3 g.) in presence of cobaltous chloride (1·0 g.), and decomposition of the complex, gave: (i) Phenylacetylene (4·0 g., 34%), b. p. 96°/100 mm., n_D^{19} 1·5485—1·5500; the mercury salt had m. p. 124—125° (Johnson and McEwen, *J. Amer. Chem. Soc.*, 1926, **48**, 469, give m. p. 124·5—125°). (ii) 1-Phenylprop-1-yne (4·7 g., 41%), b. p. 66°/15 mm., n_D^{19} 1·5615; light absorption, see Table 2 (Truchèt, *Ann. Chim.*, 1931, **16**, 395, gives b. p. 71—74°/15 mm., n_D^{18} 1·561). (iii) Diphenylbutadiyne (0·7 g.), b. p. 130° (bath temp.)/10^{-3} mm., which crystallised from alcohol in needles, m. p. and mixed m. p. with the specimen described above, 84—86°.

1-*Phenylhex*-1-*yne*.—(*a*) Reaction of butylmagnesium bromide (from 2·9 g. of magnesium) with 1-bromo-2-phenylacetylene (13·5 g.) in presence of cobaltous chloride (0·75 g.) gave 1-phenylhex-1-yne (4·9 g.), b. p. 105°/10 mm., n_D^{20} 1·5345 (Johnson, Schwartz, and Jacobs, *J. Amer. Chem. Soc.*, 1938, **60**, 1882, give b. p. 109—110°/12 mm., n_D^{20} 1·5347) (Found: C, 90·8; H, 9·05. Calc. for $C_{12}H_{14}$: C, 91·1; H, 8·9%). Light absorption: see Table 2. No diphenylbutadiyne was detected.

When the reaction was carried out at −50°, most of the materials were recovered, and a small amount of diphenylbutadiyne was isolated.

(*b*) Reaction of butylmagnesium bromide (from 3·0 g. of magnesium) with 1-iodo-2-phenylacetylene (21 g.) in presence of cobaltous chloride (0·75 g.) gave 1-phenylhex-1-yne (4·6 g.), b. p. 105°/10 mm., n_D^{23} 1·5310. No diphenylbutadiyne was detected.

(*c*) Reaction of butylmagnesium bromide (from 3·9 g. of magnesium) with 1-bromo-2-phenylacetylene (18·1 g.) in presence of cuprous chloride (0·6 g.) gave 1-phenylhex-1-yne (7·3 g.), b. p. 110°/10 mm., n_D^{21} 1·5310. No diphenylbutadiyne was detected.

Repetition of the preceding experiment without a catalyst, and decomposition of the complex, gave: (i) Phenylacetylene (6·5 g.), b. p. 130°, n_D^{26} 1·5430; the mercury salt had m. p. 124°. (ii) Butyl bromide (7·7 g.), b. p. 100°, which was converted into *S*-butylthiourea picrate, m. p. 175° undepressed on admixture with an authentic specimen.

Diphenylacetylene (*Tolane*).—Reaction of phenylmagnesium bromide (from 3·9 g. of magnesium) with 1-bromo-2-phenylacetylene (16·0 g.) in presence of cobaltous chloride (1·0 g.) gave: (i) Diphenylacetylene (5·5 g.), b. p. 90—97°/0·5 mm., which crystallised from alcohol in leaflets, m. p. 61—62° (Found: C, 94·0; H, 5·8. Calc. for $C_{14}H_{10}$: C, 94·35; H, 5·65%) (Paillard and Wieland, *Helv. Chim. Acta*, 1938, **21**, 1356, give m. p. 62°); light absorption, see Table 2. (ii) Diphenylbutadiyne (0·2 g.), m. p. 82—85° undepressed on admixture with the specimen described above.

Repetition of the preceding experiment without the catalyst led to an almost quantitative recovery of phenylacetylene; diphenylbutadiyne (0·2 g.) was also isolated.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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Mechanisms of Removal of Hydrogen from Palladium–Hydrogen by Oxidation.

By F. A. Lewis and A. R. Ubbelohde.

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The controlled removal of hydrogen from palladium–hydrogen has been studied. In solutions of strong oxidising electrolytes, removal starts without appreciable induction periods. Ceric salts give readily controlled removal. Kinetic studies are reported on the system ceric ammonium sulphate–sulphuric acid–palladium–hydrogen.

Oxidation also proceeds when palladium–hydrogen is stored under water, exposed to oxygen. But when dry specimens are stored in the open air under normal conditions, palladium wire will retain hydrogen in concentrations as high as H/Pd = 0·6 for periods of up to one year. When similar specimens are enclosed with air or oxygen in glass tubing, the hydrogen is completely removed from the palladium by oxidation. This oxidation follows an induction period whose duration is affected by many variables. In particular, the induction period can be indefinitely prolonged when steps are taken to remove water vapour from the reaction vessel. It seems likely that the hydrogen is oxidised by oxygen by an ionic mechanism.

Under moist conditions, oxidation of metals by atmospheric oxygen could involve as one of the steps the oxidation of hydrogen atoms adsorbed on the surface of the metal. These hydrogen atoms are formed by discharge of hydrogen ions from solution. When the metal contains hydrogen in solid solution, as in palladium–hydrogen alloys, this adsorbed film of hydrogen can be maintained by diffusion from the interior. Mechanisms of removal of hydrogen from palladium–hydrogen by oxidation may thus be related to a number of key processes in the physical chemistry of corrosion, and of hydrogen in metals.

After palladium has been charged with hydrogen by electrolysis, the conditions for escape are as follows. With $H/Pd > 0{\cdot}6$, hydrogen rapidly escapes *in vacuo* from the alloy even at room temperatures. With $H/Pd \leqslant 0{\cdot}6$, hydrogen is held for indefinite periods at room temperature but escapes on heating to 200°. As discussed in this paper, removal can also be achieved by various processes of oxidation.

From alloys with $H/Pd \leqslant 0{\cdot}6$ removal at room temperature takes place when the alloy is made the anode of an electrolytic cell (Nähring, *Ann. Physik*, 1934, **21**, 303; Moore, *Trans. Electrochem. Soc.*, 1939, **75**, 237; Lewis, Roberts, and Ubbelohde, *Proc. Roy. Soc.*, 1953, **220**, 279. The present work deals with the removal of hydrogen by other oxidation processes. As shown below, ceric ammonium sulphate removes hydrogen from the alloy, with simultaneous quantitative reduction of the oxidising agent. This gives one method for controlled removal of portions of the hydrogen. Rate-measurements on this process are reported.

In the extensive literature on palladium–hydrogen, conflicting statements appear on the stability of the alloy when exposed to gaseous oxygen. Some authors (Michel, Bénard, and Chaudron, *Bull. Soc. chim.*, 1943, **12**, 336) claim immediate loss of hydrogen from palladium–hydrogen on exposure to air. Others (Sieverts, *Z. physikal. Chem.*, 1914, **88**, 103; Puoduzuikynas, *Z. Physik*, 1927, **46**, 253; Norberg, *Phys. Review*, 1952, **86**, 745) report the retention of hydrogen by palladium for long periods under normal atmospheric conditions.

In the present work slow oxidation by atmospheric oxygen always occurred when palladium–hydrogen was stored under water. Although dried palladium–hydrogen retained its hydrogen for indefinite periods in the open atmosphere, yet removal of the hydrogen to form water took place, after variable induction periods, when the palladium–hydrogen was enclosed in glass vessels. Though the duration of the induction period was influenced by many variables, water must apparently always be present before reaction with atmospheric oxygen can proceed at appreciable rates. Possible mechanisms for the

removal of hydrogen from palladium by oxidation are discussed below. It seems likely that water is required because of easier oxidation of hydrogen when ionic mechanisms can play a part.

Experimental

Palladium (Johnson & Matthey) was in the form of wire of 0·27 mm. diameter, or strip 1·75 mm. wide × 0·075 mm. thick. Both wire and strip were 99·9% pure and contained as impurities: Ir, >0·05—0·1; Pt, Rh, >0·03—0·05; Cu, Ca, >0·02; Mg, >0·01; Fe, >0·005; Ag, >0·02%.

Electrolytic Charging and Direct Estimation of the Hydrogen Content.—The palladium was charged with hydrogen by electrolysis. For reasons previously discussed (Lewis, Roberts, and Ubbelohde, *loc. cit.*) the electrolyte used was a 2% solution of sodium fluoride and the current density was 1·3 amp./dm.^{2}.

Up to a dozen specimens of wire or strip 10 cm. long were mounted symmetrically in a Tufnol frame round a platinum anode and were charged simultaneously, to ensure similar conditions for the entry of hydrogen. The wire or strip was then washed with distilled water and dried with filter-paper. When a specimen was heated at 200° in an evacuated vessel of calibrated volume (Lewis *et al.*, *loc. cit.*) the pressure developed gave the Pd/H ratio in the alloy. Tests showed samples from one batch were reproducible to ±2%. This method is referred to below as " degassing analysis."

Atmospheric Oxidation of Palladium–Hydrogen in Aqueous Solution.—Charged specimens from one batch were placed under distilled water in conical flasks open to the air. By " degassing analysis " after various time intervals, it was found that hydrogen was slowly but completely removed at room temperature. The rate of removal was greatly increased if a stream of oxygen was bubbled through the water. Another four-fold increase in removal rate occurred when pure water was replaced by 2M-sodium hydroxide or 2M-sulphuric acid.

Irrespective of the pH, no loss of hydrogen could be detected if oxygen-free nitrogen was bubbled through the water instead of oxygen. All the experiments with oxidising solutions described below were therefore carried out under oxygen-free nitrogen.

Removal of Hydrogen from Palladium–Hydrogen by Oxidising Solutions.—Oxidising solutions tried were iodine in potassium iodide, potassium permanganate, and ceric ammonium sulphate in 1·0M-sulphuric acid, all 0·01M or 0·1M and standardised by established methods.

Iodine in potassium iodide. Reduction of iodine was estimated colorimetrically, by comparison with standard solutions of iodine in a simple comparator. More than 20 specimens of palladium, charged with hydrogen to concentrations up to 0·6 H/Pd, were immersed in 0·01M-solutions of iodine in potassium iodide. In all but four of these experiments no reduction of the iodine was observed. In one of four instances, reduction began after a time lag of 1 day, and in another case after a lag of 4 days. Reduction started immediately after immersion in the other two cases. No interpretation of these variable induction periods is offered at present.

Potassium permanganate. Only visual observations were made on permanganate solutions. On immersion of palladium–hydrogen in neutral or 2M-acid solutions of potassium permanganate at about 20°, flakes of manganese dioxide were rapidly formed on the surface of the palladium. These may have blocked access of fresh oxidising agent of the alloy, though further reduction was apparently not completely prevented. The precipitate gradually became dispersed through the solution. No attempts were made to follow rates of oxidation quantitatively.

Ceric ammonium sulphate. Reduction of this reagent was determined by titration. 15 Ml. of the solution of oxidising agent were placed in a number of 25-ml. stoppered flasks. Specimens were introduced either of the charged palladium–hydrogen, or of uncharged palladium (for blank experiments). At intervals, 1 ml. of solution was withdrawn and titrated against ferrous ammonium sulphate (tris-*o*-phenanthroline as indicator). Reactions were carried out in an ice-bath, or in baths kept by thermostat at 25° ± 0·1° and 50° ± 0·1°.

As with potassium permanganate, all the palladium–hydrogen specimens began to reduce ceric solutions immediately after immersion. For rate measurements, ceric salts had the advantage over potassium permanganate in that the reduction product was colourless and soluble. Control experiments showed that some reduction of the ceric solution was caused by the hydrogen-free palladium at 50° in the 1·0M-acid solution used to prevent hydrolysis of the ceric sulphate. The rate curve for 50° was corrected to allow for this. Four experimental runs were carried out at each temperature, and the results averaged. Fig. 1 shows that the results agree with first-order kinetics with respect to the concentration of ceric

ammonium sulphate during the first part of the reaction. With the possible exception of the reaction at 0°, examination for second-order kinetics by plotting C against t gave non-linear plots (not shown). The activation energy of the reaction as calculated from the slopes in Fig. 1 is as shown in the following table.

Temp.	0°	25°	50°
log k, sec.$^{-1}$	−5·54	−5·34	−4·89
E (kcal./mole)	2·9		8

By "degassing analysis" of the residual hydrogen, after removal of part by oxidation, it was verified that the amount of hydrogen lost was exactly equivalent to the amount of ceric ion reduced, for specimens containing H/Pd $>0{\cdot}6$. Specimens of palladium–hydrogen degassed when further reduction of ceric ion was no longer detected contained no hydrogen within experimental error (H/Pd $<0{\cdot}01$). As in other instances, specimens with H/Pd $>0{\cdot}6$ lost some hydrogen spontaneously as bubbles of gas.

FIG. 1. *Logarithmic unimolecular plots of oxidation rates.*

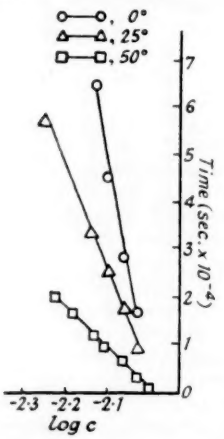
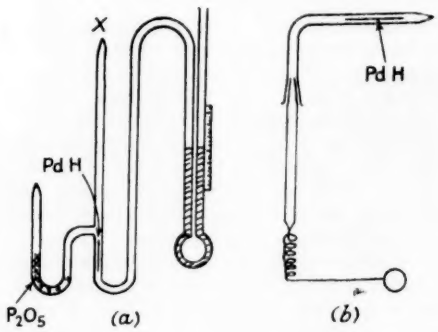


FIG. 2. *Reaction tubes for the oxidation of* Pd–H *by air.*



Preliminary experiments with 0·1M-solutions of ceric ammonium sulphate showed that removal was much faster than with 0·01M. Further studies of reaction rates were not attempted. Many other variables could obviously be explored in a complete study. The present investigations were intended as background to the observations on removal in the various circumstances described in this paper. It was considered especially important to examine whether any induction periods were shown in this system.

Stability of Palladium–Hydrogen in vacuo *and in Nitrogen.*—Experiments confirmed that the palladium wire and strip used in the present work retained hydrogen at concentrations of 0·6 H/Pd for indefinite periods at room temperatures *in vacuo* or in oxygen-free nitrogen.

Oxidation of Palladium–Hydrogen in Air.—An observation by Monckman (*Proc. Roy. Soc.*, 1888, **44**, 220) was confirmed. When palladium–hydrogen in wire form was heated in a Bunsen flame at one end, a tiny flame caused by combustion of hydrogen travelled along the wire from the point of heating. However, when the palladium–hydrogen was heated quickly to 200° after being enclosed in a Pyrex tube, the hydrogen was released as gas, similar to the effect *in vacuo*. At this temperature no detectable reaction with the air in the tube had occurred. On the temperature being then raised at one end of the palladium to red heat, by means of a Bunsen burner, an explosive reaction occurred between the hydrogen and the air.

No loss of hydrogen could be detected when charged specimens were stored in the open air at room temperature. For more detailed tests, charged specimens were enclosed in an atmosphere of air in simple containers of Pyrex glass tubing of 3—5 mm. bore (Fig. 2*a*). In special experiments, a Pyrex spiral gauge with mirror was sealed on (Fig. 2*b*) to permit continuous recording of changes in pressure by means of a light-beam falling on a rotating drum

carrying light-sensitive paper. More generally, in view of the large number of experiments carried out, it proved convenient to use a simple manometer (Fig. 2*a*). The indicator liquid in the manometer was mercury or Apiezon oil, or other liquids as indicated below. Tubes were kept in the laboratory at about 18°. Visual readings of the manometer pressure were taken at intervals. Corrections for slight fluctuations of room temperature and pressure, which might obscure the induction period, were made from observations with an apparatus of similar volume which had no alloy introduced into it.

These simple containers had side arms into which phosphoric oxide could be introduced. This avoided contamination of the walls of the container near to the specimen by phosphoric acid. Alternatively, the containers could be opened momentarily at X to introduce drops of water or hydrogen peroxide near to the palladium–hydrogen before resealing.

General Observations on the Induction Period preceding Rapid Oxidation of the Palladium–Hydrogen.—When specimens of palladium wire charged to concentrations of *ca.* H/Pd $\leqslant 0{\cdot}6$ were degassed after being in the open air for periods up to 1 year, they still contained as much hydrogen as specimens charged under the same conditions and degassed immediately after charging. Occasionally, some loss of hydrogen was observed from specimens in the form of strip, although most of these had also retained their initial content of hydrogen.

FIG. 3. *Illustrations of induction periods in the oxidation of* Pd/H *by air*

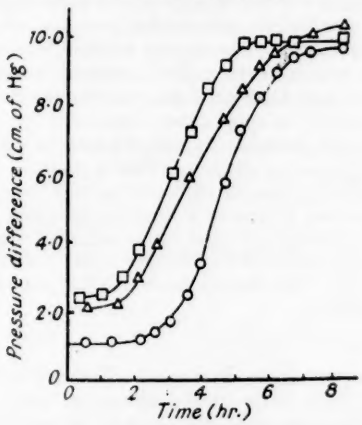
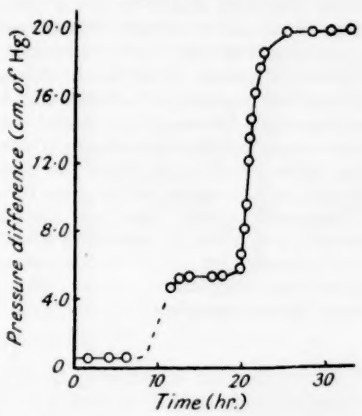


FIG. 4. *Oxidation of two specimens of* Pd/H *side by side.*



However, when specimens were enclosed as described above, pressure–time curves showed that after a variable but much shorter period the hydrogen from the palladium combined with oxygen in the air. During the period of detectable pressure changes a fine mist of water droplets was formed on the glass walls immediately around the specimen. Potassium iodide–starch being used as reagent, no hydrogen peroxide could be found in these deposited droplets. No back-pressure changes were ever observed, due to an accumulation of hydrogen peroxide followed by its catalytic decomposition with re-formation of oxygen. A few of the many curves obtained are reproduced in Fig. 3 to illustrate the general course of the reaction. By degassing the palladium after all pressure changes had ceased, any residual hydrogen was almost always found to be less than the limits of detectability (H/Pd $\geqslant 0{\cdot}01$). The volume of hydrogen gas at S.T.P. originally contained in each specimen was $\sim$3 ml.

Effect of Water on the Induction Period.—The duration of the induction period and the rate of the subsequent reaction were very variable. The effect of water was examined in some detail. Definite lengthening of the induction period was observed when the reaction tube and specimen were very carefully dried. Very great lengthening of the induction period (in almost all cases to indefinite periods) was observed when phosphoric oxide was introduced into the reaction vessel and held either in a side arm or behind a glass wool plug.

Although water seemed necessary for reaction to start, the presence of water did not result in all cases in a complete suppression of the induction period. For example, Fig. 4 shows how two specimens, side by side in the same container, reacted independently. During the distinct

interval between the ends of the two induction periods, the second specimen was intimately surrounded by the water vapour produced by the first specimen.

Apparently, many other variables also affect the induction period. Effects recorded below were less sharply conclusive and reproducible than the effect of intensive drying, but definite trends were exhibited when comparison was made over a large number of experiments under comparable conditions.

(1) Tubing bore. Increasing the bore of the tubing lengthened the induction period and decreased the rate of reaction.

(2) Manometer liquid. The induction period was lengthened, compared with mercury, when dibutyl phthalate or Apiezon oil was used as manometer liquid.

(3) Surface area and extent of cold-working of the palladium. The induction period was longer with palladium wire than with strip.

(4) Effect of ageing palladium–hydrogen. When specimens of wire with H/Pd ~0·6 had been left in the open air for about 6 months before being introduced into a reaction vessel, the induction period was indefinitely long even in the presence of water vapour. Hydrogen was, however, readily and immediately removed from these specimens by solutions of ceric ammonium sulphate.

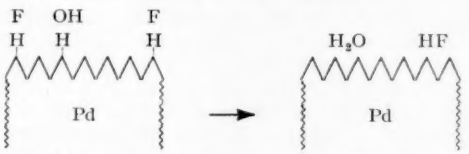
(5) Initial concentration of hydrogen in the palladium. Induction periods were shorter the higher the initial concentrations of hydrogen, up to H/Pd = 0·6.

(6) Effect of trimethylamine. This substance was tested because it is a typical anti-oxidant in oxidation chains involving peroxide radicals. When the specimens after charging were quickly dipped in trimethylamine and wiped dry before introduction into the reaction vessel, the induction period was lengthened and the rate of the subsequent reaction reduced.

(7) Effect of hydrogen peroxide. When charged specimens were quickly dipped in 100-vol. hydrogen peroxide made just alkaline and then wiped with filter-paper before introduction into a reaction vessel, the induction period was reduced and in some cases removed. Attempts were also made to introduce minute traces of hydrogen peroxide in acid, neutral, or alkaline solution, either close to, or on to the surface of a specimen already within a reaction tube. Such traces did not appear to bring the induction period preceding oxidation to an abrupt end. These observations were, however, complicated because of pressure changes resulting from decomposition of peroxide, especially when in actual contact with the metal surface. Possible effects of antioxidants added to commercial hydrogen peroxide to stabilise it are unlikely to complicate the experiments, since sufficient pure peroxide should have distilled on to the specimens, from drops placed nearby, to give a fair test.

Discussion

(1) *Electrochemical Removal of Hydrogen from Palladium–Hydrogen.*—The experiments now reported link oxidations by acid ceric sulphate with anodic oxidation previously described by a number of authors (*locc. cit.*). In anodic removal of hydrogen, the mechanism of reaction may involve adsorption of discharged atoms of F or discharged radicals OH on the surface, followed by the desorption of HF or H_2O :

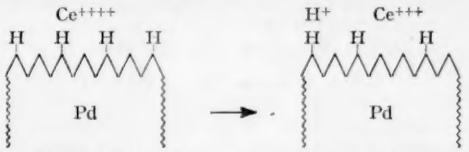


Without further evidence, it is not possible to distinguish between this process and one in which OH or F are desorbed as ions after electron transfer from proximate hydrogen :

As soon as a vacant site is formed in the surface of the alloy, it can become occupied by a fresh hydrogen atom diffusing from the interior.

It seems likely that oxidation of palladium–hydrogen by ceric sulphate is analogous in

mechanism to anodic oxidation. Either there is direct sorption of ceric ions on the surface, followed by electron transfer and desorption :



or the ceric ions produce free (OH) radicals in solution, in the oxidation–reduction equilibrium (cf. Ubbelohde, *J.*, 1935, 1605) $Ce^{4+} + OH^- \rightleftharpoons Ce^{3+} + OH$ and the adsorption of OH is followed by oxidation of hydrogen atoms on the surface precisely as in anodic discharge. The oxidation–reduction potential of ceric sulphate ($E^0 = 1{\cdot}61$ v) seems sufficient to promote such a process. The rapid increase in oxidation rate with increase in concentration of Ce^{4+} gives some support to this second possibility. It is noteworthy that in 0·01M-ceric sulphate, the rate of oxidation corresponds with a current density of 0·05 amp./dm.^{2} (if it is assumed that Faraday's law applies accurately to anodic oxidation). In 0·1M-solutions the oxidation rate corresponded approximately with 1 amp./dm.^{2}.

So far as present evidence goes, the rate of oxidation is of zero order with respect to the H/Pd ratio at low concentrations of ceric sulphate. This can be explained on either of the above mechanisms, if the controlling reaction rate refers to the chemical action of OH or Ce^{4+} at a surface always effectively covered with hydrogen atoms bonded to surface palladium atoms. This would be the case if the rate of emergence of fresh hydrogen atoms on to vacant palladium atoms in the surface is rapid compared with the other reaction rates.

(2) *Oxidation of Palladium–Hydrogen by Atmospheric Oxygen in Aqueous Solution.*— Oxidation of hydrogen in palladium–hydrogen by atmospheric oxygen may be related to the oxidation of other metals in aqueous solution. A free-radical mechanism or an ionic mechanism offers possible explanations. The processes are thought to occur at the metal surfaces, which need not, however, be uniformly covered with hydrogen. The free-radical mechanism might involve as likely steps

$$\overset{H}{\widehat{Pd}} + O_2 \rightleftharpoons \widehat{Pd} + HO_2 \quad \text{(i)}$$

$$HO_2 + H_2O \longrightarrow H_2O_2 + OH \quad \text{(ii)}$$

$$H \qquad \overset{H}{\widehat{Pd}} + OH \longrightarrow \widehat{Pd} + H_2O \quad \text{(iii)}$$

(The symbol $\widehat{Pd}$ refers to hydrogen atoms chemisorbed on palladium atoms in the surface.)

It has not yet proved possible to detect the accumulation of hydrogen peroxide, but any hydrogen peroxide is probably decomposed too rapidly catalytically by the palladium. This would agree with the observation that transitional metals are not found to exhibit the Russell effect (cf. Churchill, *Trans. Electrochem. Soc.*, 1939, **76**, 341).

Acceleration of oxidation by atmospheric oxygen when the solution is made either acid or alkaline favours an ionic mechanism, which may require regions of different potential in order that they may proceed smoothly (cf. Evans, " Introduction to Metallic Corrosion," Edward Arnold, London, 1948, p. 27) :

$$OH_3^+ + O_2 \rightleftharpoons O_2H^+ + H_2O \quad \text{(iv)}$$

$$O_2H^+ + \underset{\widehat{Pd}}{H} \longrightarrow H^+ + HO_2 + \widehat{Pd} \quad \text{(v)}$$

$$HO_2 + \underset{\widehat{Pd}}{H} \longrightarrow HO_2^- + \widehat{Pd} + H^+ \quad \text{(vi)}$$

$$HO_2^- + \underset{\widehat{Pd}}{H} \longrightarrow (OH) + OH^- + \widehat{Pd} \quad \text{(vii)}$$

$$OH + \underset{\widehat{Pd}}{H} \longrightarrow OH^- + H^+ + \widehat{Pd} \quad \text{(viii)}$$

In alkaline solutions the first steps are probably somewhat different:

$$O_2 + H\widehat{Pd} \longrightarrow O_2H + \widehat{Pd} \quad \text{(ix)}$$

$$O_2H + OH^- \longrightarrow HO_2^- + OH \quad \text{(x)}$$

$$OH + H\widehat{Pd} \longrightarrow OH^- + \widehat{Pd} + H^+ \quad \text{(xi)}$$

with the subsequent removal of H_2O_2 as at (vii) and (viii) above.

(3) *Oxidation of Palladium–Hydrogen by Atmospheric Oxygen in the Air.*—Whilst the above steps are still tentative, they throw some light on the possibilities in the gas phase. The long induction periods observed in many cases might be due to the existence of a poisoning layer of adsorbed atoms at the surface of palladium–hydrogen. Poisons from the drying agent used have been suggested in similar cases (Hinshelwood and Williamson, "The Reaction between Hydrogen and Oxygen," Clarendon Press, Oxford, 1934, p. 3; Schwab, "Catalysis," Macmillan and Co., London, 1937, p. 37). Oxygen is known to inhibit sorption of hydrogen by activated palladium (Ubbelohde, *Trans. Faraday Soc.*, 1932, **28**, 275). Presumably chemisorbed oxygen forms an adsorbed layer difficult to remove. On the principle of microscopic reversibility, if chemisorbed oxygen slows down the process $2\widehat{Pd} + H_2$ (gas) ⟶ PdH (solid) it must also slow down the reverse process. Some evidence is reported above suggesting such chemical poisoning by traces of volatile impurities in the open atmosphere, or by trimethylamine. However, the definite influence of water in shortening the induction period supports the view that water must accumulate in cracks and crevices of the metal before oxidation can proceed smoothly by an ionic mechanism. On this view the induction period would correspond with the time required to build up a system in which an ionic mechanism can proceed. Ionic oxidation itself does not seem to involve induction periods. Since water does not always immediately suppress the induction period, traces of hydrogen peroxide may be slowly formed by autoxidation in the water collected in minute crevices in the metal. So far as any hydrogen peroxide can accumulate, it could act as an electrolyte. In accordance with equations (iv) and (x) it has been verified that electrolytes furnishing hydrogen ions accelerate oxidation.

Finally, attention may be drawn to the practical consequences of this investigation. Treatment by ceric sulphate can be a very convenient method for partial withdrawal of hydrogen from palladium–hydrogen. Again, charged specimens are best kept in a dry inert atmosphere if required not to lose their hydrogen. When the metal is in a finely divided state, in the form of powder or sponge, palladium–hydrogen may be pyrophoric on exposure to air, and access to oxygen must be completely prevented at all times (Ubbelohde, unpublished observations).

THE QUEEN'S UNIVERSITY, BELFAST. [*Received, December 21st,* 1953.]

The Optical Resolution of 1 : 1′-*Dinaphthyl*-5 : 5′-*dicarboxylic Acid.*

By F. BELL and W. H. D. MORGAN.

[Reprint Order No. 5017.]

1 : 1′-Dinaphthyl-5 : 5′-dicarboxylic acid has been resolved into optically active forms; the mechanism of racemisation is discussed.

SINCE 1 : 1′-dianthryl can be obtained in optically active forms of moderate stability (Bell and Waring, *J.*, 1949, 1579) it would be expected that 1 : 1′-dinaphthyl, also, could exist in optically active forms, although possibly of lower stability.

Attempts to resolve 4 : 4′-diamino-1 : 1′-dinaphthyl and 1 : 1′-dinaphthyl-4 : 4′-dicarboxylic acid yielded negative results (Bell and Morgan, *J.*, 1950, 1963) and attention was next directed to 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid. The bromine atom of ethyl

5-bromo-1-naphthoate, easily obtained from 1-nitronaphthalene, did not react with copper at 280°, and an Ullmann reaction with 5-bromo-1-nitronaphthalene required a temperature so high for initiation that decompostion ensued. The acid was obtained from 1-naphthoic acid by Seer and Scholl's method (*Annalen*, 1913, **398**, 83) and from 1-nitronaphthalene by that of Short and Wang (*J.*, 1950, 992), and independent resolution experiments were made on the two samples.

Experiments with quinidine, quinine, cinchonine, cinchonidine, and morphine failed, probably owing to the high solubilities of the salts. However, brucine gave a less soluble salt of the (+)-acid. The rotations of solutions of the partially active (+)- and (−)-acids in dilute aqueous sodium hydroxide were sensibly unchanged overnight but were reduced to zero by heating on a steam-bath for 1 hour. The optical stability of this substituted 1 : 1′-dinaphthyl appears to be of the same order as that of 1 : 1′-dianthryl and, rather surprisingly, also of 1 : 1′-dinaphthyl-8-carboxylic and -8 : 8′-dicarboxylic acid (Stanley, *J. Amer. Chem. Soc.*, 1931, **53**, 3104; Corbellini, *Atti R. Accad. Lincei*, 1931, **13**, 702; Meisenheimer, *Ber.*, 1932, **65**, 32), but much less than that of 1 : 1′-dinaphthyl-2 : 2′-dicarboxylic acid (Kuhn and Albrecht, *Annalen*, 1928, **465**, 282) and 2 : 2′-diamino-1 : 1′-dinaphthyl (Kuhn and Goldfinger, *Annalen*, 1929, **470**, 183). Models of the Catalin type indicate that 1 : 1′-dinaphthyl-8-carboxylic and -8 : 8′-dicarboxylic acid, once optically active, should never racemise. Obviously the purely mechanical interpretation of the resolvability of diphenyls is an inadequate guide to racemisation results in this series. Such great distortion of the molecule would be required to allow free rotation about the 1 : 1′-linkage of these acids that it appears more probable that racemisation may be occasioned by a minute dissociation of such dinaphthyls into substituted naphthyl radicals. Such a process would probably be associated with a fairly high energy of activation and would agree with the observed great increase in rate of racemisation with rise of temperature.

Further, the production of a compound such as ethyl 6 : 6′-dinitrodiphenate from ethyl 1-iodo-6-nitrobenzene-2-carboxylate by an Ullmann reaction involves the union of two iodine-free residues in a specifically oriented arrangement and it is difficult to see how this could be achieved if the reaction involved any type of transition complex. Here reaction could most easily be interpreted as a union of free radicals. It must be admitted, however, that none of the reactions of the various dinaphthyls and dianthryls so far recorded in the literature appears to require for their interpretation the existence of free radicals, and, also, we failed to isolate any phenylanthracene from the product of interaction of 9 : 9′-dianthryl with dibenzoyl peroxide.

Experimental

5-Nitro-1-naphthoic acid.—(a) *Ekstrand's method* (*J. pr. Chem.*, 1888, **38**, 156). 1-Naphthoic acid (*Org. Synth.*, **11**, 80; the 1-naphthylmagnesium bromide was poured on crushed carbon dioxide; yield, 57%) (87·5 g.) and concentrated nitric acid (230 c.c.) were heated on a steam-bath for 3—4 hr., then poured on ice. The precipitated solid was collected, washed, and extracted with boiling sodium carbonate (70 g.) solution. On acidification of the extract 90 g. of mixed nitro-acids were obtained. Crystallisation from alcohol (630 c.c.) gave, first, the 5-isomer, m. p. 234—235°, as fawn needles. Further small crops were obtained by evaporation and slow cooling (total yield, 18·5 g.).

(b) *Short and Wang's method* (*loc. cit.*). 1-Nitronaphthalene was converted successively into 1-chloromethyl-5-nitronaphthalene, 1-hydroxymethyl-5-nitronaphthalene, and 5-nitro-1-naphthoic acid. Amplification of Ekstrand's description (*loc. cit.*, p. 244) of the reduction of 5-nitro-1-naphthoic acid appears desirable. The nitro-acid (18·5 g.), in a small volume of dilute ammonia solution, was added slowly to a boiling solution of ferrous sulphate (200 g. in 240 c.c. of water). Aqueous ammonia (*d* 0·880; *ca.* 100 c.c.) was added cautiously until the mixture was alkaline as indicated by the precipitate becoming jet black. The mixture was boiled vigorously for 10 min. and then filtered into glacial acetic acid (30 c.c.), pale yellow 5-amino-1-naphthoic acid (12·2 g., 78%), m. p. 212—213°, being precipitated.

5-Amino-1-naphthoic acid was converted as described by Seer and Scholl (*loc. cit.*) into 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid (m. p. 351—355°) which after being boiled with acetic

acid had m. p. 361°. The quinine, quinidine, cinchonine, cinchonidine, and morphine salts of this acid were non-crystallising and in solution had a strong green fluorescence.

Resolution of 1 : 1′-*Dinaphthyl*-5 : 5′-*dicarboxylic Acid.*—(a) *Acid from* 1-*naphthoic acid.* Brucine (1·77 g., 2 mols.) was added to a suspension of the acid (0·65 g.) in boiling ethanol (65 c.c.). The mixture was refluxed gently for ½ hr., the clear solution first obtained beginning to deposit crystals. After cooling, the insoluble portion (1·7 g.) was filtered off and the filtrate poured into dilute hydrochloric acid. The recovered 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid, m. p. 355°, had $[\alpha]_D$ −20·4° (*c*, 1·08 in 0·1N-NaOH). The crop of the brucine salt was purified by extraction with boiling ethanol (65 c.c.) and then formed a pale yellow powder, m. p. 210° (decomp.), $[\alpha]_D$ −10·4° (*c*, 2·5 in $CHCl_3$). This was decomposed by trituration with dilute hydrochloric acid to give (+)-1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid, m. p. 355°, $[\alpha]_D$ +66° (*c*, 1 in 0·1N-NaOH).

(b) *Acid from* 1-*nitronaphthalene* (the authors are indebted to Mr. R. S. Williams for this material). The acid obtained as above from the more soluble salt had $[\alpha]_D$ −55° (*c*, 1 in 0·1N-NaOH). That obtained from the less soluble salt by trituration with dilute hydrochloric and subsequent reprecipitation from solution in sodium hydroxide had $[\alpha]_D$ +41° (*c*, 1·04 in 0·1N-NaOH). Rapid determination of the rotatory power of this acid is difficult because if precipitated from a solution of the sodium salt in the cold the acid separates as a bulky, gelatinous, almost unfilterable mass whilst precipitation near the b. p. adversely affects the rotatory power.

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The Nature of Inorganic Chromatography on Cellulose Columns.

By D. E. CHALKLEY and R. J. P. WILLIAMS.

[Reprint Order No. 5028.]

A careful study of the movement of zones of ferric ions under different eluting conditions on cellulose columns suggests that the process is one of simple partition between two liquid phases.

INORGANIC chromatography on cellulose is often suggested to be a form of partition chromatography in which the cellulose acts as a support for the stationary aqueous phase while the organic phase flows through the column. No evidence has been produced to support this view, and the complexity of many chromatographic procedures has obscured the nature of the underlying process. An analysis of the latter can be made in two ways. First it might be possible to show that the movement of zones of inorganic ions on the columns in simple elution chromatograms obeys the theoretical relation deduced by Martin and Synge (*Biochem. J.*, 1941, **35**, 1358) between this movement and the bulk distribution coefficient of the individual ions between the two liquid phases. Secondly a general comparison could be made between the separations possible on cellulose columns and those obtained in bulk distribution experiments. The latter comparison is difficult, for whereas simple two-component two-phase systems, in which the phases are readily separable, are prefered in bulk extractions, phase separation is no problem in chromatograms and complex three-component two-phase systems are more often used (Wells, *Quart. Reviews*, 1953, **7**, 307). The first approach was therefore considered more profitable.

The theoretical relationship deduced by Martin and Synge (*loc. cit.*) is that the distribution coefficient is given by

$$D = \frac{[\text{M}] \text{ in mobile phase}}{[\text{M}] \text{ in non-mobile phase}} = \frac{V_a}{V_o} \frac{1}{(1/R_F - 1)} \quad . \quad . \quad . \quad . \quad (1)$$

where V_a is the volume of the stationary aqueous phase, V_o that of the mobile organic phase, and R_F is the ratio of the rate of movement of the concentration maximum of the zone of the substance M under study to that of the mobile phase, or

$$R_F = V/V_o \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where V is the volume of the mobile phase which has flowed from the column when the peak of the zone reaches the end of the column, and V_o is often called the "dead" volume of mobile phase in the column. Relation (1) can be tested in two ways. The values of D and R_F can be compared for a number of cations, one solvent system being used, or for one cation, changes being made in the solvent system. We used the latter method taking ferric ion as our test case. As we had previously determined the distribution of ferric ions between solvents containing aqueous hydrochloric acid, methanol, and ethyl ether (to be published), we investigated the behaviour of ferric ions on cellulose columns in the presence of these solvent systems.

Equation (1) holds only if the partition isotherm is linear and if the process on the column is one of pure partition between two liquid phases. We examined both conditions.

The Effect of Iron Concentration on the Partition.—The first condition can be tested in three ways: the bulk distribution should obey Nernst's law, the elution peak from the column should be symmetrical, and the R_F value should be independent of the column length. In our solvent systems (see Table), Nernst's law was obeyed at iron concentrations less than 10^{-3}M but above this very considerable deviations appear. The elution peaks obtained in the column experiments were not exactly symmetrical despite the fact that we worked at concentrations lower than 10^{-3}M but the asymmetry was small. At higher concentrations tailing peaks occurred and in such concentrated solutions as are commonly employed in inorganic chromatography, elution analysis cannot be efficient because the partition isotherms are curved. The success of inorganic chromatography on cellulose is due to large differences between the partition coefficients of the individual metals and to the accidental application of gradient elution analysis (p. 1720). The R_F did not vary with column length in our experiments.

The Part played by Adsorption.—If adsorption affects chromatography on cellulose the cations must be adsorbed on to the cellulose from the stationary phase. Thus, ferric ions should not travel down a column at the solvent front ($R_F = 1{\cdot}0$) when an *adsorption* chromatogram is run with cellulose as the adsorbent and with the stationary phase from a partition chromatogram as the mobile eluting solvent. We have carried out a number of such experiments using different aqueous phases as eluting solvents. When the acid concentration was sufficiently high to prevent formation of ferric hydroxide iron was eluted very close to the solvent front and we conclude that negligible adsorption occurs.

Equilibrium of Phases on the Column.—Before R_F values could be measured it had to be shown that the solvents on the column were in equilibrium with one another. This difficulty is not often met in chromatography but we showed that it is necessary to run large volumes of solvent through a cellulose column before the mobile and the stationary phase are in equilibrium. We packed our columns in the stationary phase which had been equilibrated with the solvent to be used as the mobile phase, but even then equilibrium was not established until large volumes of solvent had passed. In several cases we followed the acidity of the effluent and found that when our three-component solvents (Table) were used, equilibrium was reached after some 50 ml. of solvent had passed. However, if a column 20 cm. × 1 cm. is packed in the aqueous layer formed in equilibrium with pure ether at an initial aqueous acidity (HCl) of 0—5M and the ether layer is then used as the mobile phase, the acidity of the effluent changes continuously until more than a litre of solvent has passed through the column. A gradient of acidity and a gradient of water content of both phases are established along the column; such gradients greatly adjust the nature of the processes taking place (Williams, *Analyst*, 1952, **77**, 905).

The uptake of acid by the stationary phase on a cellulose column and the changes in water content of the two phases from the equilibrium value established in bulk are such that the nature of the stationary phase is unknown when a chromatogram is run. We have therefore limited our examination of the movement of ions on such partition columns to that found in solvent systems in which we had previously shown the partition to be dependent upon the acidity of the organic layer and to be extremely insensitive to changes in the aqueous layer. Over considerable ranges of acidity there is a simple relation between the acidity of the organic layer and the distribution of the ferric ion which allows the latter to be calculated from the former (to be published). It cannot be assumed that

any similar simple relationship will hold for other solvent systems or for other cation distributions and it was for this reason that we restricted attention to the ferric ion.

The Volume of the Phases on the Column.—In order to determine R_F from equation (2) V_o must be found. The simplest method uses a frontal analysis with a coloured non-partitioning dye in the mobile phase. The break-through volume of the dye front is then the dead volume of the mobile phase. Using azobenzene we found the dead volume of our columns to be 0·3 ml./ml. of column volume.

The volume of the stationary phase, V_a, was obtained by measuring the amount of liquid taken up by the cellulose. The experiment was carried out with several of the solvents which we used as stationary solvents; V_a was 0·25 $\pm$ 0·05 ml./ml.

Rate of Flow of Solvent.—If the rate of flow of the solvent is below 5 ml./hr. there is no difficulty in obtaining R_F values independent of the rate of flow. At higher rates larger R_F values are obtained and equilibrium is not established on the column. Apparently most separations on cellulose columns described in the literature are not run near to equilibrium.

To keep the column in equilibrium, the substance to be chromatographed must be put on in the mobile phase. We applied the iron as 0·2 ml. of solution of ferric chloride in the organic layer. Few inorganic ions can be applied in this way so that the column equilibrium is usually destroyed on introducing the cation solution.

The R_F Values.—After the iron had been introduced elution with the organic phase was begun and the effluent collected on a fraction collector designed for us by Mr. C. A. Baker. The fractions were analysed for iron by the thiocyanate method. The R_F values determined at different values of D are given in the Table. The plot of $1/(1/R_F - 1)$ against D is a straight line and the slope of the line V_a/V_o is 0·75 which corresponds closely with the value determined directly (see above). We therefore consider that chromatography of ferric ions, at least, is a pure partition process.

Survey of Chromatography of Other Cations on Cellulose.—We have shown above that no direct correspondence can be expected between inorganic chomatography on cellulose columns, as generally performed, and bulk partition experiments. However, the following points are noteworthy.

(1) In three-component solvent systems D may well pass through a maximum and then a minimum with changing acidity. R_F will follow the same pattern, as we have shown for the ferric ion, but these changes will occur at different acidities for each cation.

(2) A rough guide to the order of R_F of different cations is given by the order of ease of formation of the complex extracted. This guide will be of value only at low acid concentration in the solvents, as it is entirely upset by the formation of anionic complexes in the aqueous phase.

(3) The extracting powers of solvents parallel their effect on R_F values. Among solvents which are all members of the same homologous series, the lowest members extract most efficiently and the R_F value of a given cation in these solvents also increases in this order (Burstall, Davies, Linstead, and Wells, *J.*, 1950, 516; Lederer, *Analyt. Chim. Acta*, 1951, **5**, 185).

(4) Our experiments with ferric ions on cellulose led us to suppose that many separations on such partition columns depended fortuitously on a gradient of the solvent along the column. Therefore we have made a number of experiments using a deliberately imposed

R_F values for the migration of ferric ions on cellulose columns under different conditions.

[The solvents in the different experiments were made by the addition of 5 ml. of aqueous acid of initial normality, N_a^I, to methanol (7·5 ml.) and ethyl ether (25 ml.). The lighter phase was used as the mobile phase and the heavier phase was equilibrated with the adsorbent.]

N_a^I	0·05	0·10	0·19	0·32	0·39	0·46
D_{Fe}	0·015	0·03	0·07	0·16	0·23	0·33
R_F	0·04	0·08	0·10	0·18	0·24	0·29
$1/(1/R_F - 1)$	0·04	0·08	0·11	0·21	0·31	0·40

solvent gradient in the elution of cations from cellulose. The gradient is controlled by an external mixing vessel as described by Alm, Williams, and Tiselius (*Acta Chem. Scand.*,

1952, **6**, 826). The method permits the separation of cations which differ greatly in partition coefficient in one operation, *e.g.* iron, cobalt, nickel, and copper can be eluted as chlorides, whereas many of these mixtures require frequent changes of solvent with stepwise elution (Burstall *et al.*, *loc. cit.*).

As the procedure we recommend is readily adapted to many separative problems in inorganic chromatography we will defer further description until a later publication. Since this work was finished Lederer (*Nature*, 1953, **172**, 635) has described the application of the same technique in paper-sheet chromatography, showing that it has considerable advantages over the usual procedures.

The authors acknowledge the helpful criticism of Dr. H. Irving in this work.

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Synthesis of Plant-growth Regulators. Part III. ω-2-Naphthyloxyalkanecarboxylic Acids.*

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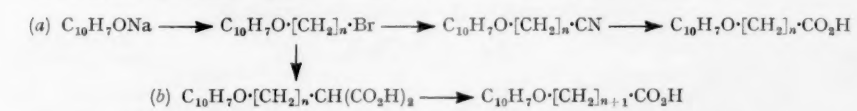
The preparation of a number of chlorine-substituted and unsubstituted ω-2-naphthyloxyalkanecarboxylic acids is described.

AN alternation in plant-growth regulating activity in homologous series of ω-substituted alkanecarboxylic acids has been reported by several workers (Thimann and Bonner, *Physiol. Reviews*, 1938, **18**, 524; Grace, *Canad. J. Res.*, *C*, 1939, **17**, 247; Synerholm and Zimmerman, *Contribn. Boyce Thompson Inst.*, 1947, **14**, 369; Fawcett, Ingram, and Wain, *Nature*, 1952, **170**, 887). The acids described in this paper belong to five homologous series of ω-2-naphthyloxyalkanecarboxylic acids. Their biological activity has been measured by the ability to induce parthenocarpic development of unpollinated tomato ovaries, and a full account will be published later (Luckwill and Woodcock, in preparation).

Two main synthetical routes were employed for the required acids :


(a) $C_{10}H_7ONa$ → $C_{10}H_7O\cdot[CH_2]_n\cdot Br$ → $C_{10}H_7O\cdot[CH_2]_n\cdot CN$ → $C_{10}H_7O\cdot[CH_2]_n\cdot CO_2H$
(b) $C_{10}H_7O\cdot[CH_2]_n\cdot CH(CO_2H)_2$ → $C_{10}H_7O\cdot[CH_2]_{n+1}\cdot CO_2H$

Where the appropriate polymethylene dibromide was readily available route (*a*) was used; in other cases a malonic ester synthesis (*b*), starting from the ω-2′-naphthyloxyalkyl bromide with two carbon atoms less than the final side-chain, led to the required acid. The β-substituted propionic acids were, however, more conveniently obtained by condensation of the sodium naphthoxide with β-propiolactone (cf. Byrde, Crowdy, and Woodcock, *Ann. appl. Biol.*, 1953, **40**, 152).

An interesting case of apparent dimorphism was observed with 6-2′-naphthyloxyhexanoic acid. Two forms, which do not mutually depress, have been obtained and all attempts at interconversion have so far failed. Both forms are equally active as agents for inducing parthenocarpy in the tomato-ovary test.

Some typical preparations are fully described in the experimental section; analytical details for all new compounds are given in the Tables.

* Part II, *J.*, 1953, 2089.

Experimental

β-2-*Naphthyloxypropionic Acid.*—β-Propiolactone (3·6 g.) was added dropwise during 10 min. to a boiling stirred solution of β-naphthol (7·2 g.) and sodium hydroxide (2 g.) in water (30 ml.). After being heated for a further 15 min., the solution was cooled, acidified, and extracted with ether. The acid, isolated from the ethereal solution by shaking it with sodium hydrogen carbonate solution and acidifying it, was washed with water and dried at 100°. It (1·8 g.) crystallised from methyl alcohol in rhombic prisms, m. p. 143—144° (Found: equiv., 216·8. Calc. for $C_{13}H_{12}O_3$: equiv., 216). Chakravarti and Dutta, (*J. Indian Chem. Soc.*, 1939, **16**, 639) give m. p. 144—145°.

3-2′-*Naphthyloxypropyl Chloride.*—β-Naphthol (7·2 g.) was added to sodium ethoxide [from sodium (1·15 g.) and ethyl alcohol (40 ml.)], and the solution added dropwise during 1 hr. to a boiling mixture of 1-bromopropyl chloride (10 ml.) and ethyl alcohol (20 ml.). After being refluxed for 4 hr., the solution was cooled, diluted with water, and extracted with ether; an ether-insoluble solid (*A*) was filtered off. The ethereal solution after being washed with sodium hydroxide and water was dried, the solvent removed, and the residue distilled. The fraction, b. p. 138—142°/0·5 mm., solidified, and the *chloride* then crystallised from light petroleum (b. p. 40—60°) in small prisms (4·2 g.), m. p. 51—52° (Found: C, 70·9; H, 5·8; Cl, 15·8. $C_{13}H_{13}OCl$ requires C, 70·8; H, 5·9; Cl, 16·1%). The solid (*A*) crystallised from benzene in nacreous plates, m. p. 146—147° (Found: C, 83·8; H, 6·0. $C_{23}H_{20}O_2$ requires C, 84·1; H, 6·1%).

3-2′-*Naphthyloxypropyl Cyanide.*—The chloride (8·7 g.) and sodium cyanide (2·5 g.) were heated in ethyl alcohol (40 ml.) under reflux for 18 hr. The alcohol was distilled off, water added, and the product extracted with ether. The residue, after removal of the ether, was distilled (b. p. 152—160°/0·5 mm.). The solid distillate of *cyanide* crystallised from ethyl alcohol–light petroleum (b. p. 40°) in nacreous plates, m. p. 41—42° (Found: C, 79·5; H, 6·2. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2%).

γ-2-*Naphthyloxybutyric Acid.*—The cyanide (7·8 g.) was hydrolysed with a boiling solution of potassium hydroxide (2·5 g.) in water (5 ml.) and ethyl alcohol (20 ml.) for 18 hr. The solution was cooled, diluted with water, and extracted with ether. Extraction of the ethereal solution with aqueous sodium hydrogen carbonate, followed by acidification of the extract gave the required acid, which crystallised from benzene–light petroleum (b. p. 40°) in aggregates of small rhombs, m. p. 122—123° (Found: C, 73·3; H, 6·1. Calc. for $C_{14}H_{14}O_3$: C, 73·0; H, 6·2%). This acid was prepared by Synerholm and Zimmerman (*loc. cit.*) who claimed it as a new compound, but it had been previously reported by Nair and Peacock (*J. Indian Chem. Soc.*, 1935, **12**, 318) who gave m. p. 122°.

δ-2-*Naphthyloxyvaleric Acid.*—A solution of the above chloride (13·6 g.) in ethyl alcohol (30 ml.) was refluxed for 6 hr. with sodiomalonic ester (from 8·4 g. of diethyl malonate and 1·2 g.

Substituted ω-2-*naphthyloxyalkanecarboxylic acids*, $C_{10}H_7O\cdot[CH_2]\cdot_nCO_2H$ (substituents in the naphthalene system).

Substituent	*n*	Route	Solvent *	M. p.	Found, %			Formula	Required, %		
					C	H	Cl		C	H	Cl
H	4	*b*	C_6H_6–*A*	111—112°	74·1	6·6	—	$C_{15}H_{16}O_3$	73·8	6·6	—
H	5	*a*	aq. MeOH	126—127	74·5	7·0	—	$C_{16}H_{18}O_3$	74·4	7·0	—
			aq. MeOH	94—95	74·8	7·0	—	$C_{16}H_{18}O_3$	74·4	7·0	—
H	6	*b*	Et_2O–*B*	96—97	74·9	7·2	—	$C_{17}H_{20}O_3$	75·0	7·4	—
H	7	*b*	*B*	91—92	75·2	7·7	—	$C_{18}H_{22}O_3$	75·5	7·7	—
H	8	*a*	Et_2O–*B*	98—99	76·4	8·0	—	$C_{19}H_{24}O_3$	76·0	8·0	—
H	9	*a*	Benzene	114—115	76·0	8·3	—	$C_{20}H_{26}O_3$	76·4	8·3	—
H	11	*b*	EtOH	96—97	77·1	8·8	—	$C_{22}H_{30}O_3$	77·2	8·8	—
3-Cl	2	—	MeOH	173—174	62·4	4·3	14·4	$C_{13}H_{11}O_3Cl$	62·3	4·4	14·2
3-Cl	3	*a*	aq. AcOH	174—175	63·3	5·0	13·3	$C_{14}H_{13}O_3Cl$	63·5	4·9	13·4
3-Cl	5	*a*	aq. MeOH	114—115	65·2	5·8	12·0	$C_{16}H_{17}O_3Cl$	65·6	5·8	12·1
3-Cl	7	*b*	aq. MeOH	74—75	67·8	6·6	11·0	$C_{18}H_{21}O_3Cl$	67·4	6·6	11·1
3-Cl	9	*a*	Et_2O–*B*	90—91	68·8	6·9	10·5	$C_{20}H_{25}O_3Cl$	68·8	7·2	10·2
1-Cl	2	—	MeOH	170—171	62·3	4·4	14·6	$C_{13}H_{11}O_3Cl$	62·3	4·4	14·2
1-Cl	3	*a*	MeOH	139—140	63·3	4·9	13·3	$C_{14}H_{13}O_3Cl$	63·5	4·9	13·4
1-Cl	5	*a*	MeOH	144—145	65·9	6·2	12·3	$C_{16}H_{17}O_3Cl$	65·7	5·8	12·1
8-Cl	3	*a*	AcOH	159—160	63·5	4·9	13·2	$C_{14}H_{13}O_3Cl$	63·5	4·9	13·4
8-Cl	5	*a*	Et_2O–*B*	122—123	65·5	6·0	12·2	$C_{16}H_{17}O_3Cl$	65·7	5·8	12·1
3 : 4-Cl_2	2	—	MeOH	168—169	54·7	3·4	25·0	$C_{13}H_{10}O_3Cl_2$	54·8	3·5	24·9
3 : 4-Cl_2	3	*a*	Dioxan	175—177	56·5	4·0	23·7	$C_{14}H_{12}O_3Cl_2$	56·2	4·1	23·7

Substituted ω-2-naphthyloxyalkyl halides and cyanides, $C_{10}H_7O\cdot[CH_2]_n\cdot X$ (substituents in the naphthalene system).

Substituent	*n*	X	Solvent *	M. p.	Found, % C	H	Halogen	Formula	Required, % C	H	Halogen
H	2	Br	*B*	94—95°	57·5	4·5	31·8	$C_{12}H_{11}OBr$	57·4	4·4	31·8
H	3	Br	*A*	56—57	59·2	5·0	29·9	$C_{13}H_{13}OBr$	58·9	4·9	30·2
H	3	Cl	*A*	51—52	70·9	5·8	15·8	$C_{13}H_{13}OCl$	70·8	5·9	16·1
H	5	Br	liquid	[1]	61·5	6·2	27·5	$C_{15}H_{17}OBr$	61·4	5·8	27·3
H	6	Br	*A*	40—41	62·5	6·3	26·2	$C_{16}H_{19}OBr$	62·5	6·2	26·1
H	8	Br	EtOH	47—48	64·6	7·1	23·6	$C_{18}H_{23}OBr$	64·5	6·9	23·9
H	10	Br	EtOH	54—55	66·0	7·4	21·9	$C_{20}H_{27}OBr$	66·1	7·4	22·0
3-Cl	3	Cl	*A*	64—65	60·9	4·8	28·0	$C_{13}H_{12}OCl_2$	61·2	4·7	27·8
3-Cl	5	Br	*A*	64—65	55·0	4·9	Cl, 10·6	$C_{15}H_{16}OBrCl$	55·0	4·9	Cl, 10·8
3-Cl	6	Br	*A*	67—68	56·1	5·6	Cl, 10·3	$C_{16}H_{18}OBrCl$	56·2	5·3	Cl, 10·4
1-Cl	3	Cl	liquid	[2]	61·4	4·8	27·7	$C_{13}H_{12}OCl_2$	61·2	4·7	27·8
1-Cl	5	Br	*A*	48—49	55·1	4·8	Cl, 10·7	$C_{15}H_{16}OBrCl$	55·0	4·9	Cl, 10·8
8-Cl	3	Cl	liquid	[3]	61·5	4·5	—	$C_{13}H_{12}OCl_2$	61·2	4·7	27·8
8-Cl	5	Br	EtOH	58—60	54·8	5·1	—	$C_{15}H_{16}OBrCl$	55·0	4·9	Cl, 10·8
3 : 4-Cl_2	3	Cl	EtOH	92—93	53·9	3·6	36·6	$C_{13}H_{11}OCl_3$	53·9	3·8	36·8
3 : 4-Cl_2	5	Br	EtOH	66—67	49·6	4·2	Cl, 19·4	$C_{15}H_{15}OBrCl_2$	49·7	4·1	Cl, 19·6
H	3	CN	EtOH–*A*	41—42	79·5	6·2	—	$C_{14}H_{13}ON$	79·6	6·2	—
H	5	CN	Et_2O–A	59—60	80·2	7·1	—	$C_{16}H_{17}ON$	80·3	7·1	—
H	8	CN	aq. MeOH	51—52	80·7	8·0	—	$C_{19}H_{23}ON$	81·1	8·2	—
H	9	CN	liquid	[4]	81·5	8·7	—	$C_{20}H_{25}ON$	81·4	8·5	—
3-Cl	3	CN	EtOH	96—97	67·9	5·1	14·6	$C_{14}H_{12}ONCl$	68·4	4·9	14·4
3-Cl	5	CN	EtOH	109—110	69·9	6·1	13·0	$C_{16}H_{16}ONCl$	70·2	5·9	13·0
1-Cl	3	CN	Et_2O–*B*	82—83	68·4	4·6	14·6	$C_{14}H_{12}ONCl$	68·4	4·9	14·5
1-Cl	5	CN	EtOH	74·5—75	70·2	5·8	13·0	$C_{16}H_{16}ONCl$	70·2	5·9	13·0
8-Cl	3	CN	EtOH	56—57	68·7	5·0	14·6	$C_{14}H_{12}ONCl$	68·4	4·9	14·5
8-Cl	5	CN	EtOH	74—76	70·1	5·7	—	$C_{16}H_{16}ONCl$	70·2	5·9	13·0
3 : 4-Cl_2	3	CN	MeOH	85—86	59·6	3·9	25·6	$C_{14}H_{11}ONCl_2$	60·0	3·9	25·4
3 : 4-Cl_2	5	CN	MeOH	81—82	62·0	4·7	23·3	$C_{16}H_{15}ONCl_2$	62·4	4·9	23·0

Substituted ω-2-naphthyloxyalkylmalonic acids, $C_{10}H_7O\cdot[CH_2]_n\cdot CH(CO_2H)_2$ (substituents in the naphthalene system).

H	3	—	Et_2O–*B*	171—172 (dec.)	66·6	5·6	—	$C_{16}H_{16}O_5$	66·7	5·6	—
H	5	—	Et_2O–*B*	153—154 (dec.)	68·2	6·2	—	$C_{18}H_{20}O_5$	68·3	6·3	—
H	6	—	AcOH	161—162 (dec.)	69·0	6·9	—	$C_{19}H_{22}O_5$	69·3	6·7	—
H	10	—	aq. AcOH	134—135	71·5	7·8	—	$C_{23}H_{30}O_5$	71·5	7·8	—
3-Cl	6	—	aq. AcOH	149—150 (dec.)	62·2	5·8	9·7	$C_{19}H_{21}O_5Cl$	62·5	5·8	9·7

1 : ω-*Bis*-2′-*naphthyloxyalkanes*, $C_{10}H_7\cdot O\cdot[CH_2]_n\cdot O\cdot C_{10}H_7$ (substituents in naphthalene system).

H	2	—	Dioxan	215—216	84·1	5·8	—	$C_{22}H_{18}O_2$	84·1	5·7	—
H	3	—	Benzene	146—147	83·8	6·3	—	$C_{23}H_{20}O_2$	84·1	6·1	—
H	5	—	*A*	74—76	84·0	7·0	—	$C_{25}H_{24}O_2$	84·3	6·7	—
H	6	—	Benzene	152—153	84·3	7·1	—	$C_{26}H_{26}O_2$	84·3	7·0	—
H	8	—	Benzene	129—130	84·2	7·5	—	$C_{28}H_{30}O_2$	84·4	7·5	—
H	9	—	C_6H_6–*A*	128—129	84·5	7·6	—	$C_{29}H_{32}O_2$	84·5	7·8	—
H	10	—	Benzene	126—127	84·5	7·9	—	$C_{30}H_{34}O_2$	84·5	8·0	—
3-Cl	3	—	C_6H_6–*A*	192—193	69·3	4·7	18·0	$C_{23}H_{18}O_2Cl_2$	69·5	4·5	17·9
3 Cl	5	—	C_6H_6–*A*	144—145	71·1	5·5	16·0	$C_{26}H_{24}O_2Cl_2$	71·1	5·5	16·2

* Solvents, other than those named are: *A* light petroleum (b. p. 40—60°); *B*, light petroleum (b. p. 60—80°).
[1] B. p. 180—184°/0·2 mm. [2] B. p. 170—172°/ 0·5 mm. [3] B. p. 162—164°/0·5 mm. [4] B. p. 180—184°/0·5 mm.

of sodium). 40% Sodium hydroxide (50 ml.) was then added, and after a further hour's refluxing the solution was cooled, diluted with water, and extracted with ether. Acidification of the alkaline layer gave the *2′-naphthyloxypropylmalonic acid*, m. p. 167° (decomp.), which crystallised from acetone–benzene in monoclinic prisms, m. p. 171—172° (decomp.) (Found: C, 66·6; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Decarboxylation was carried out at

185° for 1 hr. The *valeric acid* crystallised from benzene–light petroleum (b. p. 40°) in rhombic plates, m. p. 111—112° (Found: C, 74·1; H, 6·6. $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%).

6-2′-*Naphthyloxyhexanoic Acid.*—5-2′-Naphthyloxypentyl cyanide was hydrolysed with ethyl alcoholic potassium hydroxide as described above. When the ethereal extract was shaken with sodium hydrogen carbonate solution an insoluble sodium salt was formed which was washed with ether and decomposed with concentrated hydrochloric acid. The *acid*, isolated by ether, crystallised from aqueous methyl alcohol in wedge-shaped prisms, m. p. 94—95° (Found: C, 74·8; H, 7·0. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). In another experiment, under apparently identical conditions, the product crystallised from aqueous methyl alcohol in nacreous plates, m. p. 126—127° (Found: C, 74·5; H, 7·0%). This product did not depress the m. p. of the isomeric acid, but we have so far failed to demonstrate dimorphism by the mutual seeding of solutions in aqueous methyl alcohol. The S-*benzylthiuronium* salt from the low-m. p. form only crystallised from aqueous ethyl alcohol in rectangular prisms, m. p. 156—157° (Found: C, 68·0; H, 6·6; S, 7·5. $C_{24}H_{28}O_3N_2S$ requires C, 67·9; H, 6·6; S, 7·5%).

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*The Isolation of Oligosaccharides from Gums and Mucilages. Part II.**

By P. Andrews and J. K. N. Jones.

[Reprint Order No. 5030.]

Hydrolysis of lemon gum yields a mixture of monosaccharides, and acidic and neutral oligosaccharides, including one to which the structure 4-*O*-(4-*O*-methyl-α-D-glucuronosyl)-L-arabinose (I) has been assigned.

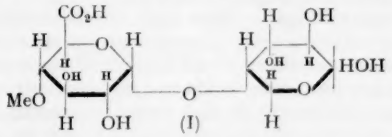
Lemon gum has been shown by Connell, Hainsworth, Hirst, and Jones (*J.*, 1950, 1696) to contain D-galactose, L-arabinose, and D-glucuronic acid. They reported a 4% methoxy-content, and this fact, together with new paper-chromatographic evidence, indicates that the glucuronic acid exists as a monomethyl derivative, probably the 4-methyl ether. These authors also isolated an aldobiuronic acid, which on methylation and hydrolysis yielded 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid and 2 : 3 : 6-tri-*O*-methyl-D-galactose, from the mixture of sugars produced when the gum was hydrolysed with boiling dilute sulphuric acid. The quantity of aldobiuronic acid obtained accounted for about a third of the total uronic acid in the gum, and it was suggested that the gum contains other aldobiuronic acid units. It is now shown that this is, in fact, the case.

Lemon gum, dissolved in N-sulphuric acid and kept at room temperature, underwent a slow hydrolysis which after some weeks had virtually ceased. The degraded gum so produced was composed of galactose and uronic acid residues only. The aldobiuronic acid described by Connell *et al.* (*loc. cit.*) was not detected amongst the sugars liberated during this hydrolysis, and therefore is undoubtedly a unit in the structure of the degraded gum. The chief monosaccharide liberated by this hydrolysis was L-arabinose, but galactose and rhamnose were also detected in trace amounts. Several oligosaccharides were produced during the degradation, two of them, both acidic, being in quantities sufficient for further examination.

The sugar acids of low molecular weight were isolated by use of an anion-exchange resin and then fractionated on a cellulose column, an acidic eluent being used. The first major component to be eluted was an *O*-methylaldobiuronic acid, to which the structure 4-*O*-(4-*O*-methyl-α-D-glucuronosyl)-L-arabinose (I) has been assigned. It was so resistant to hydrolysis that insufficient of its two component sugars could be obtained for their

* Part I, *J.*, 1953, 4090.

complete characterisation, but their rates of movement on the paper chromatogram and their colour reactions with *p*-anisidine hydrochloride corresponded with those of arabinose and 4-*O*-methylglucuronic acid. In order to elucidate further the structure of (I), it was



(I)

methylated with methyl sulphate and sodium hydroxide, and the non-reducing methylated acid was isolated, converted into its methyl ester by treatment with Purdie's reagents, and reduced to the corresponding glucosylarabinose derivative with lithium aluminium hydride. Finally, the newly-formed primary alcoholic group was methylated (Purdie's reagents), and the resultant methylated neutral disaccharide was hydrolysed with dilute acid. The resultant mixture consisted of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and 2 : 3-di-*O*-methyl-L-arabinose, which sugars were separated on a sheet-paper chromatogram and identified by their physical properties and by conversion into well-characterised crystalline *N*-phenylglycosylamine derivatives.

The isolation of these two sugars proves that in lemon gum some of the *O*-methyl-D-glucuronic acid units are united through either $C_{(4)}$ or $C_{(5)}$ of a similar number of L-arabinose residues. The high positive optical rotation ($[\alpha]_D$ +134°) of (I) indicates both that the arabinose unit is in the pyranose form, and that the 1-4′-type linkage has the α-configuration.

In addition to (I), another methoxy-containing acidic oligosaccharide was isolated from the mixture of sugar acids of low molecular weight. This one appears to be a trisaccharide, for paper-chromatographic examination indicated that on hydrolysis it yielded equimolecular amounts of (I) and arabinose. A comparison of its optical rotation ($[\alpha]_D$ *ca.* +47°) with that of (I) suggests that the additional arabinose unit is in the furanose form, but as yet there is no conclusive evidence for its structure.

Experimental

Chromatographic separations were on Whatman No. 1 paper, with the following solvent mixtures: (*a*) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (*b*) *n*-butanol–pyridine–water (10 : 3 : 3); and (*c*) *n*-butanol–ethanol–water (40 : 11 : 19) (all v/v). *p*-Anisidine hydrochloride was used as spray reagent to detect sugars. The rates of movement on the paper chromatogram of oligosaccharides are quoted relative to that of galactose, *i.e.*, they are R_{gal} values.

Optical rotations were determined at 20° ± 2° in water. Solutions were evaporated under reduced pressure. Microanalyses are by Mr. B. S. Noyes of Bristol.

Hydrolysis of the Gum.—Lemon gum (15 g.) was dissolved in cold N-sulphuric acid (150 c.c.) and the solution set aside at 20° ± 5°. Samples of the solution were withdrawn at intervals and examined on the paper chromatogram.

From 12 to 24 weeks after the start the chromatographic pattern appeared to be constant. Separation in solvent (*b*), in which uronic acids remain on the starting line, indicated the presence of much arabinose, a trace of galactose, and two neutral pentose-containing oligosaccharides, the one with R_{gal} 0·68 being present in considerable amount and the other with R_{gal} *ca.* 1·2 being present in traces only. In solvent (*a*) the picture was more complex as the uronic acids also moved on the chromatogram: the major acidic components that were present had R_{gal} 1·1 and 0·65.

After 24 weeks the gum solution was brought to pH 5 with barium hydroxide and filtered. The filtrate was concentrated to *ca.* 100 c.c., passed down a column of Amberlite resin IR120, and then down a column of Amberlite resin IR4B to remove uronic acids of low molecular weight. The effluent was neutralised with barium hydroxide, concentrated to 40 c.c., and poured into alcohol. The precipitated barium salt of the degraded gum was collected, dried, and extracted exhaustively with methanol. The yield of degraded gum was 6 g.; on hydrolysis it gave galactose and uronic acid derivatives, including a trace of an *O*-methyluronic acid, but no pentose. Concentration of the filtrate from the barium salt gave a syrupy mixture of sugars (6·5 g.) which partly crystallised. After trituration with methanol, crystalline L-arabinose

(0·4 g.), m. p. and mixed m. p. 158°, was filtered off. The filtrate was concentrated and the resulting syrup examined chromatographically [solvent (*b*)]. It consisted of arabinose (mainly), the pentose-containing disaccharide with R_{gal} 0·68, and traces of galactose, rhamnose, and two other pentose-containing saccharides (R_{gal} 1·2 and 0·35).

The Acids of Low Molecular Weight.—These were displaced from the column of Amberlite resin IR4B by elution with N-sulphuric acid. The effluent was neutralised with barium hydroxide solution and filtered, and the filtrate passed down a column of Amberlite resin IR120. The effluent contained a mixture of the ash-free uronic acids and was concentrated to dryness at 25° (yield, 1·5 g.). Chromatographic examination of this mixture [solvent (*a*)] indicated 4-*O*-methylglucuronic acid, an acidic disaccharide (I) with R_{gal} 1·1 and an acidic tri(?)saccharide with R_{gal} 0·65.

The syrup (1·5 g.) was placed on a cellulose column (14″ × 1″) and fractionally eluted with ethyl acetate–acetic acid–water (9 : 2 : 1 v/v). 4-*O*-Methyl-D-glucuronic acid (?) and traces of arabinose were first eluted followed by the *aldobiuronic acid* (I) (0·43 g.), which had R_{gal} 1·1 in solvent (*a*) and $[\alpha]_D$ +134° (*c*, 4·3) (Found: OMe, 10·4. $C_{12}H_{20}O_{11}$ requires OMe, 9·1%). The solvent was changed to ethyl acetate–acetic acid–water (9 : 2 : 2 v/v), and a slower moving component (yield, 0·9 g.) having R_{gal} 0·65 [in solvent (*a*)] was then eluted, admixed with a little of (I). The mixture had $[\alpha]_D$ +47° (*c*, 8·0) (Found: OMe, 6·0. Calc. for $C_{17}H_{28}O_{15}$: OMe, 6·6%). Hydrolysis of this fraction with dilute acid gave arabinose and a roughly equivalent amount of the aldobiuronic acid (I), detected chromatographically. The uronic acids remaining on the cellulose column were eluted with water (yield, 0·2 g.). Chromatographic examination indicated the presence in this material of three slow-moving uronic acid-containing fragments [R_{gal} 0·65, 0·42, and 0·25 in solvent (*a*)].

The aldobiuronic acid (I) was hydrolysed with 2N-sulphuric acid at 100° for 24 hr. Paper-chromatographic examination of the very dark hydrolysate indicated arabinose and 4-*O*-methylglucuronic acid but mainly unchanged (I).

Methylation of (I). The aldobiuronic acid (I) (0·42 g.) was methylated with 30% sodium hydroxide and methyl sulphate in the usual manner. The acidic product (0·47 g.), isolated by continuous chloroform extraction of the reaction mixture after acidification with sulphuric acid, was converted by treatment with Purdie's reagents into its methyl ester (yield, 0·46 g.) which was then reduced with lithium aluminium hydride by adding it dropwise in ethereal solution to a solution of this reagent in ether (yield of glucosylarabinose derivative, 0·28 g.). Unchanged methylated aldobiuronic acid (0·12 g.) was recovered by acidifying the reaction mixture with sulphuric acid and extracting it continuously with chloroform. The *glucosylarabinose derivative* was further methylated with Purdie's reagents, and the product distilled [yield, 0·25 g.; b. p. 170° (bath temp.)/1 mm.] (Found: OMe, 48·8. $C_{18}H_{34}O_{10}$ requires OMe, 52·9%).

The methylated disaccharide (0·24 g.) was hydrolysed in boiling N-hydrochloric acid: $[\alpha]_D$ +108° ⟶ + 74° (constant value, 7½ hr.). The cooled solution was neutralised with silver carbonate and filtered. The filtrate was concentrated to a syrup (0·19 g.) consisting of two sugars, which were separated on a sheet of filter paper by using solvent (*c*), and were isolated in the usual manner. The faster-moving component (0·116 g.) was identical with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose. After recrystallisation from ether–light petroleum (b. p. 60—80°) it had m. p. and mixed m. p. 90°, and the derived *N*-phenylglucosylamine had m. p. and mixed m. p. 137° after recrystallisation from ethanol. The slower-moving fraction (0·07 g.) (Found: OMe, 34·2. Calc. for $C_7H_{14}O_5$: OMe, 34·8%), having R_G 0·82 in solvent (*a*), was identical with 2 : 3-di-*O*-methyl-L-arabinose. It had $[a]_D$ +98° (*c*, 2·7), and when it was heated with alcoholic aniline *N*-phenyl-L-arabinosylamine 2 : 3-dimethyl ether was produced, m. p. and mixed m. p. 138° (Found: N, 5·5. Calc. for $C_{13}H_{19}O_4N$: N, 5·5%).

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neo*Kestose: A Trisaccharide Formed from Sucrose by Yeast Invertase.*

By D. Gross, P. H. Blanchard, and D. J. Bell.

[Reprint Order No. 5032.]

A non-reducing trisaccharide, synthesised during the action of yeast invertase preparations on sucrose, has been isolated by chromatography on a carbon–Celite column together with ~10% of the known isomeric trisaccharide, Gl α—β2-Fru*f*1—β2-Fru*f*. The new substance is composed of two D-fructose and one D-glucose radicals. From analysis of the cleavage products of the mixed methylated sugars the following structure has been assigned to the new trisaccharide; *O*-β-D-fructofuranosyl(2→6)-α-D-glucopyranosyl(1→2) β-D-fructofuranoside. It appears to be formed by enzymic transfer of a β-D-fructofuranosyl radical to sucrose. The common name *neo*kestose is suggested. Confirmation is thus provided that invertase will transfer β-D-fructofuranosyl radicals to the primary alcoholic group of D-glucopyranose as well as to those of D-fructofuranose.

A previous communication (Albon, Bell, Blanchard, Gross, and Rundell, *J.*, 1953, 24) reported the isolation and characterisation of one of the several trisaccharides synthesised by yeast invertase preparations acting on sucrose. In Bacon and Edelman's nomenclature (*Arch. Biochem.*, 1950, **28**, 467) this was "Component III" and was named kestose (II) (de Whalley, *Int. Sugar J.*, 1952, **54**, 127). We have since tried to isolate a sufficient amount of another non-reducing trisaccharide, "Component II," which according to preliminary work was known to be formed along with kestose and to consist likewise of two fructose and one glucose radical (White and Secor, *Archiv Biochem. Biophys.*, 1952, **36**, 490). Component II was present in the incomplete enzymic hydrolysate of sucrose at a concentration far lower than kestose; since the R_F values of Components III and II are close, the separation of sufficient material for structural analysis and determination of some physical constants did not appear to be simple. On a large cellulose column (Albon *et al.*, *loc. cit.*) only a small proportion of Component II was recovered in (apparently) homogeneous fractions, whilst the bulk of it was found in fractions mixed mainly with kestose, "Component I," and sucrose.

Preliminary small-scale attempts to separate Component II on charcoal–Celite columns (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677) proved more successful and revealed an interesting reversal of the sequence of eluted components in that Component II appeared in the eluate after Component III (kestose).

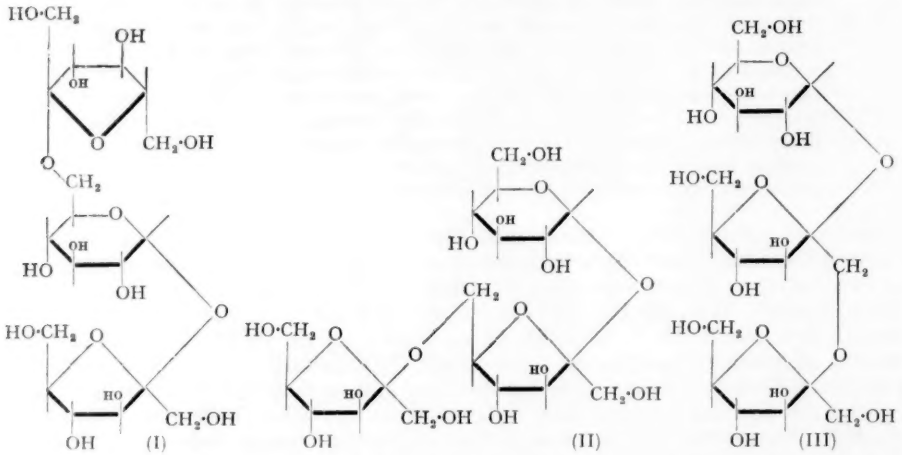
It was thought that this effect itself combined with the recently described "gradient elution" technique (Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826; Bacon and Bell, *J.*, 1953, 2528) might facilitate a satisfactory separation. A 50% solution (w/w) sucrose solution, "50% hydrolysed" by a yeast invertase preparation at pH 4·6, subjected to chromatographic fractionation by this technique, yielded Component II in a "chromatographically pure state," *i.e.*, paper-chromatographic examination of the material recovered showed it to be identical with Component II and to give a single spot.

The product could not be crystallised from water, methanol, or ethanol; it was obtained as a white, non-reducing, amorphous powder by grinding the dried eluate with dry acetone; after drying to constant weight a very hygroscopic material was obtained, having $[\alpha]_D^{20}$ +22·2° (in H_2O). Hydrolysis to completion by yeast invertase yielded 2 mols. of fructose and 1 mol. of glucose per mol. of trisaccharide.

Methylation of "Component II," as for kestose (Albon *et al.*, *loc. cit.*) and for its isomeric fructosylsucrose (Bacon and Bell, *loc. cit.*), yielded a product whose analysis suggested a hendeca-*O*-methyltrisaccharide. When the acid hydrolysate (0·05N-sulphuric acid) was analysed on a silica partition column (Bell and Palmer, *J.*, 1949, 2522; Albon *et al.*, *loc. cit.*) two clear-cut fractions were obtained. The first was expected to contain only 1 : 3 : 4 : 6-tetra-*O*-methylfructofuranose and the second only 2 : 3 : 4-tri-*O*-methyl-D-glucose. How-

ever, the physical constants of both fractions indicated that neither was homogeneous (cf. Bell and Palmer, *J.*, **1952**, 3763) and paper chromatography confirmed this. The first fraction was assayed as containing ~90% of 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose contaminated by ~10% of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose. The second fraction was assayed as containing ~90% of 2 : 3 : 4-tri-*O*-methyl-D-glucose and ~10% of 3 : 4 : 6-tri-*O*-methyl-D-fructose. It therefore was clear that " Component II," as isolated above, was not a homogeneous trisaccharide.

However, examination of Component II by high-voltage paper electrophoresis of carbohydrates in borate buffers (Gross, *Nature*, **1953**, **172**, 908) revealed the presence of a minor



" spot " as well as a major " spot "; the latter must have represented the bulk of the material. While the mobility of the minor spot was slightly lower than that of kestose, that of the major spot was considerably lower, thus affording an easy and complete separation of it from either of the two former compounds (Gross, *Nature*, **1954**, **173**, 487). While this work was in progress Dr. J. S. D. Bacon informed us that separation of Component II into 2 constituents, II_1 and II_2, had been achieved by the gradient-elution technique on a carbon–Celite column. A sample of II_2 (received from Dr. J. S. D. Bacon) showed the same electrophoretic behaviour as the major spot and a sample of II_1 corresponded to the minor spot. By this time it was too late to attempt to separate Component II on the basis of the new information, since the bulk of it had already been subjected to methylation. On the other hand our preparation and that of Bacon need not have been identical in their proportions of II_2 and II_1 since the conditions for incubation of the original solutions were different and might have caused the presence of a larger amount of II_1 in Bacon's case. The concentration of II_1 (~5—8%) in our product was estimated by visual comparison with a series of standards, but contamination, regrettable though it was, did not however seriously affect the determination of the structure of the main component, the so-called " II_2." The results of the methylation–hydrolysis–chromatographic procedure thus confirmed the findings of paper electrophoresis of the sugar–borate complexes.

It can be stated with certainty, after indubitable characterisation of the major components of each fraction, that approximately 90% of our " Component II " formed by the action of yeast-invertase preparations on sucrose consists of a new trisaccharide having the structure *O*-β-D-fructofuranosyl(2→6)-α-D-glycopyranosyl(1→2) β-D-fructofuranoside (I), and that the 10% impurity consists of *O*-α-D-glucopyranosyl(1→2)-β-D-fructofuranosyl-(1→2) β-D-fructofuranoside (III) (Bacon and Bell, *loc. cit.*, Bacon, *Biochem. J.*, in the press). The β-fructofuranosyl linkages would almost certainly follow from the known specificity of the invertases. It therefore seems clear that this experiment has confirmed the hypothesis

of Edelman and Bacon (*Biochem. J.*, 1951, **49**, 529), Fischer *et al.* (*Helv. Chim. Acta*, 1951, **34**, 1132), Bacon (*Biochem. J.*, 1952, **50**, xviii), and Whelan and Jones (*Biochem. J.*, 1953, **54**, xxxiv) that invertases (whatever their origin) have a property in common, namely, the ability to transfer β-D-fructofuranosyl radicals to acceptors which are (*a*) water molecules or (*b*) molecules of primary alcohols.

The nomenclature of new compounds always presents a problem. The first of the present series, namely, Gl α-β-2 Fru*f* 6—β2-Fru*f* (II), has been called kestose. Gl α—β 2-Fru*f* 1—β2-Fru*f* (III) is so-far unnamed. (I) cannot logically be called *iso*kestose since the name *iso*sucrose has been adopted for an isomer having linkages anomerically different from sucrose. The name kestose, having thus become established, presents a difficulty. It is therefore suggested that the substance (II) hitherto known as kestose be known as 6-kestose, the substance characterised by Bacon and Bell (*loc. cit.*) (III) as 1-kestose, and the substance (I) which is the subject of the present communication as *neo*kestose.

Experimental

Specific rotations were determined in water in a 2-dm. tube unless otherwise stated. Evaporations were done below 45° with adequate pH control.

The following values for $[\alpha]_D^{20}$ and n_D^{20} were used as standards: (*a*) 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose: $[\alpha]_D^{20}$ +81·5° (Greville and Northcote, *J.*, 1952, 1945), n_D^{20} 1·4555 (present work); (*b*) 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose: $[\alpha]_D^{20}$ +30·3°, n_D^{20} 1·4506 (Bell, *J.*, 1953, 1231); (*c*) 2 : 3 : 4-tri-*O*-methyl-D-glucose: $[\alpha]_D^{20}$ +78·7°, n_D^{20} 1·4700 (Greville and Northcote, *loc. cit.*); (*d*) 3 : 4 : 6-tri-*O*-methyl-D-fructose: $[\alpha]_D^{20}$ +29·5°, n_D^{20} 1·4651 (Bell, *loc. cit.*).

Preparation of Crude Component II.—An undialysed commercial invertase preparation ["Sumasuco" Invertase Concentrate (Sugar Manufacturers Supply Co., London)] (2·5 ml.) was allowed to act at 20° for 45 min. on a solution of sucrose (27·5 g.) in water (22·5 ml.) and 0·2M-acetate buffer (2·5 ml.) of pH 4·6. These conditions were chosen to give "50% inversion." The enzyme was then inactivated by boiling and the solution stored in an ice-box.

Large-scale Fractionation.—For fractionation by "gradient elution," three active carbons were tried; "activated charcoal" (British Drug Houses Ltd.) "active carbon No. 130" (Sutcliffe, Speakman & Co. Ltd.), and "Darco G 60" (Atlas Powder Co., New York). Active carbon No. 130 was finally chosen, as it gave a neutral eluate (as did also Darco G 60) and was not noticeably inferior to the others in resolving power. A glass tube was packed with a carefully mixed aqueous slurry of 160 g. of active carbon No. 130 and 160 g. of Celite No. 535 (Johns Manville Co. Ltd.) to form a column 70 mm. in diam. and 225 mm. high. It was first washed with water (pH of eluate 6·8), then with 30% industrial alcohol, and again with water. After reaction the sucrose solution (27 ml.) was placed on top of the column, allowed to soak in, and eluted with water of steadily increasing alcohol content. This was done by connecting the liquid on top of the column through a narrow syphoning tube with a closed 2-l. flask containing water and fitted with an electrically driven stirrer running in Polythene bearings. This flask was connected through a syphoning tube with another 2 l. flask containing 47·5% aqueous ethanol (v/v). This concentration was calculated to give a gradient reaching 30% alcohol content after 2 l. of solvent had left the first flask.

The flow rate was maintained at 60 ml./hr. and the average volume of the automatically collected fractions was 15 ml. The resolving power of the column was first tested with a mixture containing 5·5 g. of sucrose (after reaction), an amount well below the expected "loading capacity" of the column. Monosaccharides were eluted by the first 1380 ml. Mixed fractions containing disaccharides emerged up to 1770 ml., then fractions containing a mixture of disaccharides (mainly sucrose) and kestose, up to 1900 ml. After a very small gap, Component II emerged in chromatographically "homogeneous" fractions up to 2500 ml.

As the aim of this work was to obtain the maximum quantity of "Component II," the column was thereafter overloaded with 27·5 g. of "reacted sucrose." A consequent decrease in resolving efficiency necessitated the discarding of 10 overlapping fractions which contained mainly sucrose with some kestose and Component II.

After evaporation of the bulked "homogeneous" fractions to a thick syrup and their redissolution in water, a solid residue was left. This appeared to be silica originating from the column. Only after repeated evaporation and extraction with water could this contaminant be eliminated. The composition of the carbohydrate finally obtained was checked by elementary analysis.

The yields of Component II from five runs were combined and evaporated to a thick syrup. This was dissolved in water (5 ml.) and rechromatographed on a carbon–Celite column (described above). Paper chromatography of highly concentrated samples of the rechromatographed Component II revealed the presence of small amounts of sucrose and a very small amount of a substance appearing in the position of Component IV. To eliminate these contaminants, the material (1·8 g.) was dissolved in *iso*propanol–butanol–water (7 : 1 : 2 by vol.) (65 ml.) and passed through a powdered celluose column, 45 mm. in diam. and 250 mm. high (Gross and Albon, *Analyst*, 1953, **78**, 191), fractions of 15 ml. being collected. Component II was present in fractions No. 56—72, which were evaporated to a thick syrup which was then dissolved in methanol. After evaporation, the residue (in water, 30 ml.) was filtered several times through kieselguhr to eliminate finely dispersed cellulose, evaporated to a syrup, and tested by paper chromatography. No trace of the above-noted contaminants could be detected. Repeated attempts to crystallise Component II failed. The syrup was ground with dry acetone and filtered, and the solid dried to constant weight under reduced pressure at 70°, giving 1·37 g., $[\alpha]_D^{20} = +22{\cdot}2°$ (*c*, 2·34) (Found: C, 42·3; H, 6·6. $C_{18}H_{32}O_{16}$ requires C, 42·9; H, 6·4%). The substance was very soluble in both water and methanol and was non-reducing to Fehling's solution and ammoniacal silver nitrate under mild conditions. It was converted into a mixture of glucose and fructose by yeast invertase or dilute acid. On complete hydrolysis by yeast invertase, $[\alpha]_D^{20}$ of the mixture agreed with that of a mixture of two parts of fructose and one of glucose.

Methylation of the Trisaccharide.—This (711 mg.) was methylated as for kestose (Albon *et al.*, *loc. cit.*), one methyl sulphate and three methyl iodide treatments being given. The final *product*, a colourless syrup (730 mg.; 78·7%—average loss per methylation ~5%, had n_D^{20} 1·4616) (decrease for rise of 1°, 0·00034), $[\alpha]_D^{20}$ −28·0° (*c*, 9·6) (Found: C, 53·1; H, 8·4; OMe, 51·1. $C_{29}H_{54}O_{16}$ requires C, 52·9; H, 8·2; OMe, 51·8%).

Hydrolysis Products of the Methylated Trisaccharide (cf. Albon *et al.*, *loc. cit.*).—The methyl derivative (410 mg.) was heated in 0·05N-sulphuric acid (25 ml.) at 100° until a constant $[\alpha]_D^{20}$ was observed (*l*, 4). The value of +46·4° was higher than that found for kestose and the isometric trisaccharide synthesised by mould invertase (Bacon and Bell, *loc. cit.*) and indicated that the hydrolysis mixture had a different composition. From the evidence obtained later, +46·4° agrees exactly with a mixture of two moles of 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose and one of 2 : 3 : 4-tri-*O*-methyl-D-glucose (3 : 4 : 6-tri-*O*-methyl-D-fructose and its 1 : 3 : 4 : 6-tetramethyl homologue have, of course, closely similar $[\alpha]_D$'s).

Chromatography of the mixed hydrolysis products (350 mg.) on a silica column gave two clear-cut fractions. The toluene eluate (240 mg.) had $[\alpha]_D^{20}$ +35·2°, n_D^{20} 1·4518. Paper chromatography showed that the main component was a hexulose running exactly as 1 : 3 : 4 : 6-tetra-*O*-methylfructose but that a small amount of an aldose, running exactly as 2 : 3 : 4 : 6-tetra-*O*-methylglucose, was also present. The $[\alpha]_D^{20}$ and n_D^{20} values noted above agree with a 9 : 1 mixture of these two sugars. The tetramethylfructose was identified as the crystalline " tetramethylfructofuronamide " (Haworth, Hirst, and Nicholson, *J.*, 1927, 1513).

The chloroform–butanol eluate (110 mg.) from the column consisted chiefly of an aldose running identically with 2 : 3 : 4-tri-*O*-methylglucose, and contaminated with a hexulose running identically with 3 : 4 : 6-tri-*O*-methylfructose. The $[\alpha]_D^{20}$ and n_D^{20} values of this fraction (+74° and 1·4690) correspond to an approximately 9 : 1 mixture of the aforementioned sugars. The structure of the trimethylaldose was confirmed by the preparation from this fraction of the aniline derivative of 2 : 3 : 4-tri-*O*-methyl-D-glucose (Peat, Schluchterer, and Stacey, *J.*, 1939, 581), m. p. 148—149° (from ether) not depressed on admixture with the derivative prepared from chromatographically pure sugar.

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The Constitution of a Wheat-straw Xylan.

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Fractionation of wheat-straw hemicellulose yielded a xylan, devoid of arabinose residues, but containing uronic acid residues (*ca.* 3%). Hydrolysis of the methylated polysaccharide gave 2 : 3 : 4-tri-*O*-methyl-D-xylose (2·4%), 2 : 3-di-*O*-methyl-D-xylose (93%) and 2-*O*-methyl-D-xylose (3·4%), together with some 2-*O*-methyl-3-*O*-(2 : 3 : 4-tri-*O*-methyl-D-glucuronosyl)-D-xylose. It is concluded that this xylan has a straight chain of 40—45 D-xylopyranose residues with a single D-glucopyranuronic acid residue linked as a side-chain through position 3.

The lignified tissues of grasses and straws yield, on alkaline extraction after delignification, hemicelluloses containing D-xylose residues together with 5—10% of L-arabinose residues. In some hemicelluloses D-glucuronic acid residues are also present. Recent work in this laboratory has shown that at least two molecular types are present in esparto grass: a xylan, devoid of arabinose residues, consisting of a singly branched chain of 75 (±5) D-xylopyranose units (Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289); and an araboxylan in which at least the majority of L-arabinose residues are present as side-chains attached to a main chain of 1 : 4-linked D-xylopyranose residues (Aspinall, Hirst, Moody, and Percival, *J.*, 1953, 1631). Another xylan containing no arabinose residues has been isolated from the cell-wall of ripe pears. This polysaccharide was shown to contain 115 (±5) D-xylopyranose units in a singly branched chain but in addition to carry a terminal D-glucopyruronic acid unit at one point (Chanda, Hirst, and Percival, *J.*, 1951, 1240). The present investigation was undertaken to determine the structure of the xylan from wheat straw, a material known to be rich in pentosan.

Wheat-straw hemicellulose was extracted from the delignified straw with cold aqueous sodium hydroxide. Hydrolysis of the polysaccharide indicated the presence of arabinose (6·2%) in addition to xylose residues. After repeated precipitations, as the copper complex, with Fehling's solution, had failed to give a xylan devoid of arabinose residues, the arabinose-rich fraction was removed by extraction of the hemicellulose with hot 70% aqueous alcohol, leaving behind a xylan which gave only a trace of arabinose (*ca.* 0·5%) on hydrolysis.

The xylan was methylated under nitrogen with sodium hydroxide and methyl sulphate, and subsequently with methyl iodide and silver oxide, to give a product which was fractionated in boiling chloroform–light petroleum to give a methylated xylan. This was hydrolysed successively with methanolic and with aqueous hydrochloric acid, and the resulting sugars were separated on cellulose. The following sugars were isolated and characterised as crystalline derivatives: (1) 2 : 3 : 4-tri-*O*-methyl-D-xylose (2·4%); (2) 2 : 3-di-*O*-methyl-D-xylose (93%); and (3) 2-*O*-methyl-D-xylose (3·4%). In addition a tetramethyl aldobiuronic acid (*ca.* 1%) was isolated, which after reduction with lithium aluminium hydride (Lythgoe and Trippett, *J.*, 1950, 1983) followed by hydrolysis and chromatographic separation gave 2-*O*-methylxylose and 2 : 3 : 4-tri-*O*-methylglucose. The tetramethylaldobiuronic acid, which had a high rotation ($[\alpha]_D^{20}$ +97·5°) suggestive of an α-glycosidic linkage, was attacked by sodium metaperiodate (consumption, 0·8 mol. of periodate in 26 hr.) but no formic acid was produced. It seems probable, therefore, that the aldobiuronic acid was the same as that isolated from methylated pear cell-wall xylan (Chanda, Hirst, and Percival, *loc. cit.*), namely, 2-*O*-methyl-3-*O*-(2 : 3 : 4-tri-*O*-methyl-D-glucopyruronosyl)-α-D-xylose. Quantitative chromatography indicated that tri-, di-, and mono-methylxylose were present in the ratio of 1 : 34 : 1.

Vigorous hydrolysis of the wheat-straw xylan gave only one acidic substance, which travelled on the chromatogram at the same rate as glucuronic acid. Under similar conditions of hydrolysis (see Aspinall, Hirst, and Mahomed, succeeding paper) residues of 4-*O*-methyl-D-glucuronic acid are partly demethylated to D-glucuronic acid but the methyl-glucuronic acid may still be detected chromatographically. It is probable therefore that

only D-glucuronic acid residues are present in the xylan. Furthermore the low methoxyl content of the polysaccharide suggested that few, if any, uronic acid residues were present as the methyl ether. The discrepancy between the determined uronic anhydride (3·2%) in the xylan and the amount of tetramethylaldobiuronic acid (mol. % *ca.* 1) isolated from the hydrolysis of the methylated xylan may arise from decomposition of uronic acid residues during hydrolysis or from loss of the acidic components during deionisation of the hydrolysate.

A molecular-weight determination by the isothermal-distillation method (by the courtesy of Dr. C. T. Greenwood) gave a value of 8000 ± 500 (degree of polymerisation 47—53) for the methylated xylan. This value, taken together with the value of one non-reducing terminal group per 40—45 xylose residues obtained from the methylation data, suggests that wheat-straw xylan comprises an unbranched chain of xylose residues. Although the presence of some monomethylxylose would be expected from under-methylation of the polysaccharide and/or demethylation during hydrolysis of the methylated polysaccharide, it is interesting that the monomethylxylose consisted almost entirely of the 2-*O*-methyl isomer. Hydrolysis of some aldobiuronic acid units would be expected and it is probable that some of the 2-*O*-methyl-D-xylose was produced in this way.

During the present investigation the results of structural investigations of wheat-straw hemicellulose have been published elsewhere. Without attempting the isolation of a xylan containing no arabinose residues, Adams (*Canad. J. Chem.*, 1952, **30**, 698) studied the structure of a wheat-straw hemicellulose and on the basis of methylation data put forward a structure consisting of a chain of 32 1 : 4-linked D-xylopyranose residues to which are attached 5 L-arabofuranose and 3 D-glucopyruronic acid residues linked through position 3. In addition to the higher proportion of uronic acid residues, it was later suggested by Bishop (*ibid.*, 1953, **31**, 134), investigating the aldobiuronic acid 3-*O*-D-glucopyruronosyl-D-xylose isolated on hydrolysis of the same hemicellulose, that every third uronic acid residue was present as the monomethyl ether. In other respects this hemicelluose appears similar to our wheat-straw xylan: (*a*) the molecular dimensions are of the same order; and (*b*) the side-chains are linked to the main chain through position 3 of the xylose residues. In the light of our present work and of the previous structural investigations on esparto hemicelluloses it seems probable that Adams and Bishop's wheat-straw hemicellulose consists of a mixture of molecular species, ranging from a xylan carrying glucuronic acid but no arabinose side-chains to a highly branched araboxylan.

The present investigation indicates that this xylan, which is only one component of wheat-straw hemicellulose, contains a straight chain of 1 : 4-linked β-D-xylopyranose residues, to one of the non-terminal residues of which a D-glucopyruronic acid residue is linked through position 3. This xylan, therefore, differs in its fine structure from both esparto and pear cell-wall xylans; it resembles pear cell-wall xylan in containing a D-glucuronic acid residue linked to the main chain through position 3, but differs in molecular size and in having an unbranched chain of xylose residues.

Experimental

The following solvents (v/v) were used to separate the sugars and their derivatives: (A) butanol–benzene–pyridine–water (5 : 1 : 3 : 3, top layer), (B) butanol–ethanol–water (4 : 1 : 5, top layer), and (C) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4).

Isolation of Wheat-straw Xylan.—Wheat straw (variety " White Victor," cut in September 1950; 500 g.) was extracted successively with benzene and methanol, and was then delignified by Wise's method (*Ind. Eng. Chem. Anal.*, 1945, **17**, 63). The holocellulose (318 g.) was extracted with sodium hydroxide solution (4%), the extract acidified with glacial acetic acid, and the crude xylan precipitated by addition of an equal volume of ethanol. The polysaccharide was purified by five successive precipitations of the copper complex formed on addition of Fehling's solution to a solution in aqueous sodium hydroxide (4%). Further purification was effected by two extractions with boiling aqueous ethanol (70%; v/v). The purified xylan (29·6 g.) had $[\alpha]_D^{20}$ −93° (*c*, 0·21 in N-sodium hydroxide) [ash (as sulphate), 0·74; lignin 0·4; uronic anhydride, 3·2; OMe, 0·4%]. Chromatographic examination of the

hydrolysate (Hirst and Jones, *J.*, 1949, 1659) in solvent A showed the presence of xylose (88%) and arabinose (0·5%).

Methylation of Wheat-straw Xylan.—Xylan (18·4 g.) was methylated ten times with methyl sulphate and sodium hydroxide, and the product was fractionated by dissolution in boiling chloroform–light petroleum (b. p. 60—65°) mixtures. The two main fractions were further methylated twice with methyl iodide and silver oxide, and the products combined and fractionated as before, to give a main fraction, soluble in boiling chloroform–light petroleum (30 : 70) (9·4 g.) {OMe, 38·2%; $[\alpha]_D^{14}$ −82·7° (*c*, 0·45 in $CHCl_3$)}.

Hydrolysis of Methylated Xylan.—The methylated xylan (5·0 g.) was refluxed successively with methanolic hydrogen chloride (300 c.c.; 0·5%) for 24 hr. and with hydrochloric acid (300 c.c.; 0·5N) for 16 hr. The hydrolysate was neutralised with Amberlite resin IR-4B, and the solution concentrated to a syrup (4·9 g.). Quantitative paper chromatography (Hirst, Hough, and Jones, *J.*, 1949, 298) in solvent B showed the presence of tri-, di-, and mono-methyl xylose in the ratio 1 : 34 : 1.

Separation of Methylated Sugars.—The syrup (4·9 g.) was fractionated on cellulose (90 × 4 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum (b. p. 100—120°)–*n*-butanol (7 : 3) saturated with water as eluant, to give four fractions.

Fraction 1. The syrup (144 mg.) did not crystallise and hypoiodite oxidation indicated 79% of aldopentose. A sample (5 mg.) was rehydrolysed and chromatographic examination of the hydrolysate in solvent B showed the presence of 2 : 3-di- and 2 : 3 : 4-tri-*O*-methylxylose. The syrup therefore contained some (*ca.* 20%) methyl 2 : 3-di-*O*-methylxyloside.

The syrup (133 mg.) was rehydrolysed with N-hydrochloric acid (20 c.c.) on the water-bath for 6 hr. {$[\alpha]_D^{20}$ + 23 ⟶ +20° (5 hr., const.)}. After neutralisation with silver carbonate the resulting syrup (130 mg.) was fractionated on cellulose (50 × 1·4 cm.) as before, to give fractions 1*a* (101 mg.) and 1*b* (25 mg.). Fraction 1*a* after recrystallisation from dry ether had m. p. and mixed m. p. (with authentic 2 : 3 : 4-tri-*O*-methyl-D-xylose) 89° and $[\alpha]_D^{16}$ +20° (*c*, 0·9 in H_2O) (Found: OMe, 48·2. Calc. for $C_8H_{16}O_5$: OMe, 48·4%). The derived 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. and mixed m. p. 101°. Fraction 1*b* was identified as 2 : 3-di-*O*-methyl-D-xylose by conversion into its aniline derivative, m. p. and mixed m. p. 122°.

Fraction 2. The syrup (4·18 g.) had $[\alpha]_D^{20}$ +22·9° (*c*, 1·49 in H_2O), n_D^{20} 1·4694 (Found: OMe, 33·9. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Chromatographic examination showed only 2 : 3-di-*O*-methyl-D-xylose, and hypoiodite oxidation indicated 98·4% purity. The syrup partially crystallised when seeded and had m. p. 77—78°. The sugar was identified by conversion into 2 : 3-di-*O*-methyl-*N*-phenyl-D-xylosylamine, m. p. and mixed m. p. 122—123°, and into 2 : 3-di-*O*-methyl-D-xylonamide, m. p. and mixed m. p. 132°.

Fraction 3. The syrup (139 mg.) crystallised and after recrystallisation from methanol had m. p. and mixed m. p. with authentic 2-*O*-methyl-D-xylose 135—136°, and $[\alpha]_D^{19}$ +30° (*c*, 1·6 in H_2O) (Found: OMe, 18·4. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Chromatographic examination showed only 2-*O*-methyl-D-xylose, and hypoiodite oxidation indicated 99% purity. The identity of the sugar was confirmed by conversion into 2-*O*-methyl-*N*-phenyl-D-xylosylamine, m. p. and mixed m. p. 123—124°.

Fraction 4. Elution of the cellulose column with water gave a solid (308 mg.) incompletely soluble in ethanol, methanol, and water. Chromatographic examination in solvent B showed two spots [R_G 0·05 and 0·09—0·10 (dipolar)], and demethylation (Hough, Jones, and Wadman, *J.*, 1950, 1702) gave xylose, 2-*O*-methylxylose, and a trace of 2 : 3-di-*O*-methylxylose. A sample (10 mg.) was heated in a sealed tube at 100° for 6 hr. with methanolic hydrogen chloride, and the solution neutralised with silver carbonate and taken to dryness. An ethereal solution of the resulting syrup was treated with lithium aluminium hydride as described by Chanda, Hirst, and Percival (*loc. cit.*) and chromatographic examination of the hydrolysate showed the presence of 2-*O*-methyl-D-xylose and 2 : 3 : 4-tri-*O*-methyl-D-glucose.

The remainder of fraction 4 (270 mg.), which was contaminated with inorganic material, was purified by dissolution in hot methanol and the resulting syrup was heated on the water-bath for 5 hr. with N-hydrochloric acid (20 c.c.). After neutralisation with silver carbonate, the hydrolysate was fractionated on filter sheets with solvent B, to give fractions 4*a* (20 mg.) and 4*b* (72 mg.). Fraction 4*a* was shown chromatographically to consist of 2 : 3-di-*O*-methyl-D-xylose only. Fraction 4*b* had $[\alpha]_D^{16}$ +97·5° (*c*, 0·72 in H_2O) (Found: OMe, 32·2%; equiv. 350. Calc. for $C_{15}H_{26}O_{11}$: OMe, 32·4%; equiv., 382).

Fraction 4*b* (13 mg.) was heated with methanolic hydrogen chloride (2 c.c.; 1%) for 6 hr. and neutralised in the usual way. The resulting ester glycoside was reduced with lithium

aluminium hydride (Chanda, Hirst, and Percival, *loc. cit.*). The 2-*O*-methyl-D-xylose and 2 : 3 : 4-tri-*O*-methyl-D-glucose formed on hydrolysis of the product were separated chromatographically in solvent B, and estimation by hypoiodite oxidation (Chanda, Hirst, Jones, and Percival, *loc. cit.*) showed them to be present in the ratio of 1·1 : 1. The aldobiuronic acid (53·6 mg.) was converted into the sodium salt and oxidised with 0·25M-sodium metaperiodate solution (3 c.c.), and the periodate consumed after 26 hr. estimated by Fleury and Lange's method (*J. Pharm. Chim.*, 1933, **17**, 107, 196) (Found : 0·8 mol. per $C_{15}H_{26}O_{11}$ unit). Examination of the products of periodate oxidation by the method of Buchanan, Dekker, and Long (*J.*, 1950, 3162) showed that no formic acid was produced.

Chromatographic Examination of the Acidic Fraction from Xylan Hydrolysis.—Xylan (20 g.) was heated with N-sulphuric acid (400 c.c.) at 100° for 7 hr. and the hydrolysate neutralised by passage through a column of Amberlite resin 1R-4B. The resin was washed with 2N-sulphuric acid, and then with water until the eluate was free from sulphate ions. The eluate was neutralised with barium carbonate and the filtrate concentrated to a syrup (A), chromatographic examination of which showed the presence of xylose and an aldopolyuronic acid. Syrup (A) was poured into ethanol, the resulting precipitate was removed, and the solution taken to dryness to give a pale yellow solid (B). The solid (B) which contained xylose and the water-soluble barium salt of an aldopolyuronic acid was hydrolysed with 2N-sulphuric acid (2 c.c.) at 100° for 8 hr. The hydrolysate was partially neutralised with barium carbonate, and the filtrate examined chromatographically, showing the presence of xylose, glucuronic acid, and glucurone but the absence of 4-*O*-methylglucuronic acid.

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Hemicellulose A of Beechwood (Fagus sylvatica).

By G. O. ASPINALL, E. L. HIRST, and R. S. MAHOMED.

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Beech hemicellulose A has been shown to contain residues of D-xylose and 4-*O*-methyl-D-glucuronic acid (by conversion into 4-*O*-methyl-D-glucose). The methylated polysaccharide gave on hydrolysis 2 : 3 : 4-tri-*O*-methyl-D-xylose, 2 : 3-di-*O*-methyl-D-xylose, 3-*O*-methyl-D-xylose, and 3-*O*-methyl-2-*O*-(2 : 3 : 4-tri-*O*-methyl-D-glucopyruronosyl)-D-xylose in the molar ratio of 1 : 60 : 7 : 7. A structure is proposed for the hemicellulose which has a straight chain of *ca.* 70 1 : 4-linked β-D-xylopyranose residues with every tenth residue carrying a terminal 4-*O*-methyl-D-glucopyruronic acid residue linked through position 2.

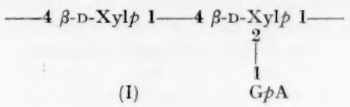
ANALYTICAL studies of the hemicelluloses of hard woods have shown that these polysaccharides consist mainly of xylose residues, but, in addition, evidence for the presence of a monomethylhexuronic acid has been obtained (cf. O'Dwyer, *Biochem. J.*, 1939, **33**, 713; 1940, **34**, 149). It was of interest, therefore, to investigate the fine structure of a polysaccharide of this type, particularly in the light of structural studies on the glucuronic-acid-containing xylans from the cell-wall of ripe pears (Chanda, Hirst, and Percival, *J.*, 1951, 1240) and wheat straw (Aspinall and Mahomed, preceding paper).

For the present investigation a quantity of the hemicellulose A isolated from European beech wood (*Fagus sylvatica*) was kindly placed at our disposal for structural investigations by Mr. I. R. C. McDonald of the Forest Products Research Laboratory, Princes Risborough (for details of the isolation see McDonald, *J.*, 1952, 3183). It may be recalled that the hemicellulose was obtained by direct alkaline extraction of the extractive-free wood instead of from the "holocellulose" fraction obtained after delignification of the wood. In view of the work of Timell and Jahn (*Svensk Papperstidning*, 1951, **24**, 831), who showed that the polysaccharides of paper birch were degraded during chlorite delignification, and of Jayme and Hank (*Cellulose-chem.*, 1943, **21**, 127) and Bublitz (*Tech. Assoc. Pulp Paper*

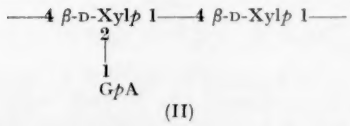
Ind., 1951, **34**, 427), who showed that polysaccharides are present in the chlorite delignification liquors of spruce wood, it was felt advisable to carry out these structural investigations on material prepared without delignification.

The beech hemicellulose A, $[\alpha]_D^{20}$ −89·4° (*c*, 0·35 in N-sodium hydroxide), gave on hydrolysis xylose (81·6%) and a trace of rhamnose (*ca.* 0·4%). In addition, the presence of uronic anhydride (9·5%) and of a significant methoxyl content (1·7%) suggested that *O*-methylhexuronic acid residues might also be present. Methylation of the polysaccharide and fractionation of the product gave methylated beech hemicellulose A {$[\alpha]_D^{19}$ −75° (*c*, 0·23 in $CHCl_3$)}. Separation of the products of hydrolysis of the methylated polysaccharide on cellulose gave tri-, di-, and mono-*O*-methylxylose and a tetra-*O*-methylaldobiuronic acid in the molar ratio of 1 : 60 : 7 : 7. The neutral sugars were identified by the formation of crystalline derivatives as 2 : 3 : 4-tri-*O*-methyl-, 2 : 3-di-*O*-methyl-, and 3-*O*-methyl-D-xylose respectively.

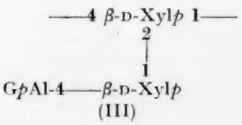
The acidic fraction was identified as 3-*O*-methyl-2-*O*-(2 : 3 : 4-tri-*O*-methyl-α-D-glucopyruronosyl)-D-xylose in the following way. Reduction of the methyl ester glycoside with lithium aluminium hydride (Lythgoe and Trippett, *J.*, 1950, 1983) followed by hydrolysis and chromatographic separation gave 3-*O*-methyl-D-xylose and 2 : 3 : 4-tri-*O*-methyl-D-glucose in the molar ratio of 1·15 : 1·0. The sugars were identified by conversion into 3-*O*-methyl-D-xylosazone and methyl 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranoside respectively. That the glucuronic acid residue was linked through position 2 and not position 4 of the xylose residue was shown by the following observations: (*a*) further methylation of the aldobiuronic acid followed by reduction with lithium aluminium hydride and hydrolysis gave 2 : 3 : 4-tri-*O*-methyl-D-glucose, 3 : 4-di-*O*-methyl-D-xylose (chromatographically separable from 2 : 3-di-*O*-methyl-D-xylose), and 3-*O*-methyl-D-xylose together with a trace of 2 : 3 : 4-tri-*O*-methyl-D-xylose; (*b*) periodate oxidation of the derived 3 : 4-di-*O*-methylxylonic acid gave no formaldehyde, whereas authentic 2 : 3-di-*O*-methyl-D-xylonic acid yielded formaldehyde under similar conditions. The chromatographic identification of a trace of 2 : 3 : 4-tri-*O*-methyl-D-xylose indicates that some aldotriuronic acid was also present in the acidic fraction. The trimethylxylose could only have arisen from a trisaccharide unit derived from the polysaccharide as in (I).



(I)



(II)



(III)

Trisaccharide units (II) and (III) would have given rise to 2 : 3-di-*O*-methylxylose on further methylation followed by hydrolysis. This observation provides further evidence that the uronic acid residues are linked directly to the main chain of xylose residues as in (I) and are not linked through a side-chain as in (III).

The acidic components in beech hemicellulose A were shown to be 4-*O*-methyl-D-glucuronic acid residues by conversion into 4-*O*-methyl-D-glucose. From hydrolysis of the polysaccharide a crude aldobiuronic acid having a significant methoxyl content was isolated. Chromatographic examination showed that vigorous hydrolysis of the aldobiuronic acid yielded xylose, glucuronic acid, and 4-*O*-methylglucuronic acid. Conversion of the aldobiuronic acid into its methyl ester glycoside, followed by reduction with sodium borohydride and hydrolysis of the product gave xylose and 4-*O*-methyl-D-glucose, the latter sugar being identified as the corresponding osazone. 4-*O*-Methyl-D-glucuronic acid has also been isolated from the hydrolysis of aspen wood (*Populus tremuloides*) by Jones and Wise (*J.*, 1952, 2750) and of *Eucalyptus regnans* wood by Stewart and Foster (*Nature*, 1953, **171**, 792). It appears therefore to be a common constituent of wood hemicelluloses.

These results indicate that beech hemicellulose A consists of a linear chain of *ca.* 70 1 : 4-linked D-xylopyranose units with approximately every tenth xylose unit carrying a 4-*O*-methyl-D-glucuronic acid unit linked as a side-chain through position 2. This conclusion is supported by a molecular-weight determination by the isothermal distillation method (by the courtesy of Dr. C. T. Greenwood and Mrs. H. Zinkiewicz) which gave a value of 11,100 ± 500 (degree of polymerisation, 66—72) for the molecular weight of the methylated hemicellulose. It is difficult to explain the isolation of a large quantity (*ca.* 10%) of monomethyl xylose. Ionophoretic examination of this fraction showed it to consist almost entirely of the 3-*O*-methyl isomer whereas random undermethylation of the polysaccharide and demethylation during hydrolysis would be expected to yield more equal quantities of the two possible isomers. It is interesting that, in the case of wheat-straw xylan (Aspinall and Mahomed, *loc. cit.*) where branching of the glucuronic acid residue occurs through position 3 of the xylose residue, the monomethyl xylose isolated on hydrolysis of the methylated polysaccharide, consisted almost entirely of the 2-*O*-methyl isomer. No methyl ethers of rhamnose were isolated, so it would appear that the rhamnose obtained from hydrolysis of the polysaccharide arose either from a contaminating glycoside or from an associated polysaccharide. It will be recalled that L-rhamnose was isolated by Jones and Wise (*loc. cit.*) from the hydrolysis of aspen wood.

Beech hemicellulose A resembles most closely the polyuronide hemicellulose of New Zealand flax (*Phormium tenax*) (McIlroy, Holmes, and Mauger, *J.*, 1945, 796; McIlroy, *J.*, 1949, 121) in that an acid residue is linked to every tenth residue of the xylan chain. It is not known, however, whether the acidic residue in the latter case are of D-glucuronic acid or of 4-*O*-methyl-D-glucuronic acid. Beech hemicellulose differs from hemicelluloses of the xylan type previously examined in these laboratories in that branching to the main chain of xylose units occurs through position 2. In the araboxylan from esparto grass (Aspinall, Hirst, Moody, and Percival, *J.*, 1953, 1631) the L-arabofuranose units and in pear cell-wall xylan (Chanda, Hirst, and Percival, *loc. cit.*) and wheat-straw xylan (Aspinall and Mahomed, *loc. cit.*) the D-glucopyruronic acid units are linked to the xylan chain through position 3. The linkage through position 2 has also been found in the hemicelluloses of aspen wood by Jones and Wise (*J.*, 1952, 3389), who isolated 2-*O*-(4-*O*-methyl-D-glucopyruronosyl)-α-D-xylose from the products of hydrolysis. It is clear that hemicelluloses of the xylan type differ markedly amongst themselves in their fine structure and that further investigations are required to unravel their complex relations.

Experimental

The solvents (A, B, and C) used to separate the sugars and their derivatives were those detailed in the preceding paper.

The polysaccharide was prepared, and kindly made available, by Mr. I. R. C. MacDonald of the Forest Products Research Laboratory, Princes Risborough (see *J.*, 1952, 3183). It was received as a fine white powder, $[\alpha]_D^{20}$ −89·4° (*c*, 0·35 in N-NaOH) (Found : OMe, 1·7; uronic anhydride, 9·5; lignin, 1·9%). Chromatographic examination of the hydrolysate (Hirst and Jones, *J.*, 1949, 1659) in solvent A showed the presence of xylose (81·6%) and (*ca.* 0·4%) of rhamnose.

Methylation of Beech Hemicellulose A.—Hemicellulose A (20 g.) was methylated twelve times with methyl sulphate and sodium hydroxide and four times with methyl iodide and silver oxide. The product (14·6 g.; OMe, 38·2%) was fractionated in boiling chloroform–light petroleum (b. p. 60—65°) mixtures to give a main fraction (12·7 g.) {OMe, 38·6%; $[\alpha]_D^{19}$ −75° (*c*, 0·23 in $CHCl_3$), $[\alpha]_D^{18}$ −113° (*c*, 1·25 in *m*-cresol)}.

Hydrolysis of Methylated Hemicellulose A and Separation of Methylated Sugars.—Methylated hemicellulose A (5·0 g.) was hydrolysed successively with 1·5% methanolic hydrogen chloride (500 c.c.) for 14 hr. and N-hydrochloric acid (200 c.c.) at 100° for 12 hr. (constant rotation). Evaporation after neutralisation with silver carbonate yielded a syrup (4·75 g.). The syrup (3·9 g.) was fractionated on cellulose (90 × 4 cm.) (Hough, Jones, and Wadman, *J.*, 1949, 2511) with light petroleum (b. p. 100—120°)–*n*-butanol (65 : 35), saturated with water as eluant. Three discrete fractions, 1 (22 mg.), 2 (46 mg.), and 3 (56 mg.), were obtained, but thereafter all fractions were contaminated by the acidic component and the column was eluted with water

to give three further fractions, **4** (0·121 g.), **5** (2·988 g.), and **6** (0·321 g.) (recovery, 91%). Partial separation of fraction 4 was effected by dissolving it in water (10 ml.), neutralising the solution with barium carbonate, and exhaustively extracting it with chloroform. The aqueous solution was deionised with Amberlite resin IR-100 to give an acidic fraction **4***a* (63 mg.). The chloroform extract gave fraction **4***b* (35 mg.), which consisted mainly of dimethylxylose but also contained some of the acidic component. Fractions **4***b* and **5** were combined and refractionated on cellulose, with solvent B as eluant, to give fractions **7** (2·108 g.) and **8** (0·390 g.); elution with water gave fraction **9** (0·242 g.) (recovery, 91%).

Examination of the Neutral Fractions.—Fraction **1**. The syrup crystallised and had m. p. 63°, $[\alpha]_D^{16}$ −47·3° (*c*, 0·15 in H_2O). The substance was non-reducing and after hydrolysis of a sample with N-hydrochloric acid at 100° for 3 hr., chromatographic examination of the hydrolysate showed only 2 : 3-di-*O*-methylxylose. It is concluded that the substance was methyl 2 : 3-di-*O*-methyl-β-D-xylopyranoside.

Fraction **2**. The syrup crystallised completely when seeded with 2 : 3 : 4-tri-*O*-methyl-D-xylose and after recrystallisation from ether had m. p. and mixed m. p. 89°, $[\alpha]_D^{20}$ +22° (*c*, 0·9 in H_2O) (Found: OMe, 48·2. Calc. for $C_8H_{16}O_5$: OMe, 48·4%). Hypoiodite oxidation indicated 99% purity and the derived 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. and mixed m. p. 98—99°.

Fractions **7** *and* **8***a*. Fraction 7 and fraction 8*a* (see below) were shown to be chromatographically identical and were combined. The syrup had $[\alpha]_D^{15}$ +22·7° (*c*, 1·1 in H_2O), and hypoiodite oxidation indicated 97—98% purity (Found: OMe, 34·5. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). The syrup crystallised slowly when seeded with 2 : 3-di-*O*-methyl-D-xylose and, separated on a porous tile, then had m. p. and mixed m. p. 78°. The derived 2 : 3-di-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. and mixed m. p. 123°.

Fraction **8**. Chromatographic examination of the syrup showed the presence of two sugars and separation on cellulose (50 × 3 cm.) with light petroleum (b. p. 100—120°)–*n*-butanol (7 : 3), saturated with water as eluant, gave fractions 8*a* (112 mg.) and 8*b* (252 mg.). Fraction 8*a* was combined with fraction 7 (see above). Fraction 8*b*, a syrup which did not crystallise when seeded with 3-*O*-methyl-D-xylose, had $[\alpha]_D^{20}$ +17° (*c*, 0·8 in H_2O), and hypoiodite oxidation indicated a purity of 97% (Found: OMe, 18·5. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Paper ionophoresis (Consden and Stanier, *Nature*, 1952, **170**, 1069) showed the presence of 3-*O*-methyl-D-xylose and of a trace of 2-*O*-methyl-D-xylose. The derived 3-*O*-methyl-*N*-phenyl-D-xylosylamine had m. p. 136°.

Examination of the Acidic Fractions.—Fractions 4*a*, **6**, and **9** were chromatographically similar and were combined. Fraction 3 behaved differently on the chromatogram and was non-acidic (Found: OMe, 34·9. Calc. for $C_{15}H_{26}O_{11}$: OMe, 32·5%), but after hydrolysis with 0·5N-hydrochloric acid (50 c.c.) at 100° for 3 hr. was chromatographically identical with the other acidic fractions, and all the acidic fractions were combined.

The combined acidic fractions (0·682 g.) had $[\alpha]_D^{19}$ +51·5° (*c*, 0·78 in H_2O) (Found: OMe, 32·3%; equiv., 399. $C_{15}H_{26}O_{11}$ requires OMe, 32·5%; equiv., 382).

Reduction with Lithium Aluminium Hydride.—The acid (210 mg.) was refluxed with methanolic hydrogen chloride for 6 hr., neutralised, and taken to dryness. The resulting syrup was dissolved in dry ether (75 c.c.), and lithium aluminium hydride (200 mg.) was added during 3 hr. to the refluxing solution. Excess of hydride was destroyed by addition of water, and the solution was acidified with 2N-sulphuric acid and extracted with chloroform (3 × 50 c.c.). The chloroform extract was taken to dryness and the syrup was hydrolysed with 0·5N-hydrochloric acid (50 c.c.) for 7 hr. at 100°. After neutralisation with silver carbonate, the hydrolysate was shown chromatographically to contain sugars travelling at the same rate as 3-*O*-methyl-D-xylose and 2 : 3 : 4-tri-*O*-methyl-D-glucose. The aqueous extract from the reduction was taken to small volume, hydrolysed with N-sulphuric acid (10 c.c.) for 5 hr. at 100°, neutralised with barium carbonate, and taken to a syrup. The syrup was dissolved in methanol, filtered from inorganic material, taken to dryness, and deionised in aqueous solution with Amberlite resins IR-120 and IR-4B. Chromatographic examination of the resulting syrup showed the same two sugars as from the chloroform extract; the sugars from both chloroform and aqueous extracts were therefore combined to give a syrup (163 mg.).

This was fractionated on filter sheets with solvent B, to give fractions *a* (67 mg.) and *b* (79 mg.). Chromatographic and ionophoretic examination of fraction *a* showed only 3-*O*-methylxylose, and the syrup crystallised partly when seeded with 3-*O*-methyl-D-xylose. The crystals had m. p. and mixed m. p. 86—88°, $[\alpha]_D^{20}$ +19·5° (*c*, 0·51 in H_2O) (Found: OMe, 18·5. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). The derived 3-*O*-methyl-D-xylosazone had m. p. and

mixed m. p. 172°. Fraction *b* was identified as 2 : 3 : 4-tri-*O*-methyl-D-glucose by conversion into the methyl β-D-pyranoside, m. p. and mixed m. p. 92—93°.

Methylation and Reduction with Lithium Aluminium Hydride.—The acid (111 mg.) was converted into the methyl ester glycoside which was methylated twice with methyl iodide and silver oxide. The product was reduced with lithium aluminium hydride as described previously and the resulting syrup was hydrolysed with 0·5N-hydrochloric acid (25 c.c.) for 7 hr. at 100°. After neutralisation with silver carbonate the hydrolysate was taken to dryness, to give a syrup (56 mg.), chromatographic examination of which showed the presence of 2 : 3 : 4-tri-*O*-methylglucose, 3 : 4-di-*O*-methylxylose, 3-*O*-methylxylose, and a trace of 2 : 3 : 4-tri-*O*-methylxylose. Chromatographic separation of the sugars with solvent B, followed by hypoiodite oxidation (Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289), showed 2 : 3 : 4-tri-*O*-methylglucose, 3 : 4-di-*O*-methylxylose, and 3-*O*-methylxylose to be present in the molar ratio 1 : 0·95 : 0·48. The solutions resulting from the hypoiodite oxidation of 2 : 3 : 4-tri-*O*-methylglucose, 3 : 4-di-*O*-methylxylose, and an authentic sample of 2 : 3-di-*O*-methyl-D-xylose were each oxidised with sodium metaperiodate solution for 48 hr., the excess of periodate was destroyed with sodium arsenite solution, and the resulting solutions were tested for formaldehyde with phenylhydrazine hydrochloride and potassium ferricyanide (cf. Chanda, Hirst, Percival, and Ross, *J.*, 1952, 1833). Formaldehyde was produced from 2 : 3 : 4-tri-*O*-methylglucose and 2 : 3-di-*O*-methyl-D-xylose but not from 3 : 4-di-*O*-methylxylose.

The Acidic Fraction from the Hydrolysis of Beech Hemicellulose A.—Hemicellulose A (10 g.) was heated with N-sulphuric acid (100 c.c.) at 100° for 6 hr. and, after cooling, the supernatant liquid was neutralised with barium carbonate, filtered, and set aside (I). The residue was heated with N-sulphuric acid (100 c.c.) for a further 4 hr. and the resulting solution was neutralised with barium carbonate, filtered, and combined with (I). The combined solutions were concentrated to a syrup which was poured into methanol to give a supernatant liquid (II) and a brown solid (III). The solid (III) was reprecipitated from aqueous solution with excess of methanol, washed with methanol, and dried; the washings were added to (II). Chromatographic examination of the reprecipitated solid (III) after removal of barium ions with Amberlite resin IR-120 showed an aldobiuronic acid and xylose to be present.

Further precipitates were obtained from the liquid (II) by the addition of ethanol and concentration of the resulting supernatant liquor to a syrup which was poured into ethanol. These solids were chromatographically similar to solid (III). The combined solids were reprecipitated several times from aqueous solution with methanol and dried (yield, 1·1 g.). A small sample was dried from aqueous solution for analysis (Found : OMe, 4·9. Calc. for barium monomethylaldobiuronate : OMe, 7·6%. Equiv. of resulting acid, 384. Calc. for $C_{12}H_{20}O_{11}$: equiv., 340). The crude barium aldobiuronate (70 mg.) was heated with methanolic 16% hydrogen chloride (5 c.c.) for 20 hr. at 70—80°, neutralised with silver carbonate, and taken to a syrup, which was hydrolysed with 0·5N-hydrochloric acid (2 c.c.) and isolated in the usual manner. Chromatographic examination of the hydrolysate in solvents B and C showed xylose, 4-*O*-methylglucuronic acid, and glucuronic acid to be present.

Reduction with Sodium Borohydride.—Crude barium aldobiuronate (2·3 g.) was converted into the methyl ester glycoside by refluxing methanolic 2% hydrogen chloride (60 c.c.) during 5 hr. After neutralisation with silver carbonate the resulting syrup was dissolved in water (150 c.c.), and sodium borohydride was (1·5 g.) added. The mixture was shaken for 16 hr. at room temperature, acidified with glacial acetic acid to pH 4, and was filtered. The filtrate was made 1·5N with respect to hydrochloric acid and heated for 6 hr. at 100°. After neutralisation with silver carbonate the hydrolysate was deionised with Amberlite resins IR-120 and IR-4B and taken to a syrup. Chromatographic examination showed the presence of xylose, 4-*O*-methylglucose, and a trace of glucose. Part of the syrup (200 mg.) was separated on filter sheets with solvent B, and the 4-*O*-methyl-D-glucose was identified by conversion into 4-*O*-methyl-D-glucosazone, m. p. and mixed m. p. 153—154°. Examination by the *X*-ray powder photograph method, by the kindness of Dr. C. A. Beevers, confirmed the identity of the osazone.

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UNIVERSITY OF EDINBURGH. [*Received, January 22nd,* 1954.]

Studies in the Synthesis of Cortisone. Part VIII. A Wagner–Meerwein Rearrangement involving Rings C and D of the Steroid Nucleus.*

By J. Elks, G. H. Phillipps, D. A. H. Taylor, and L. J. Wyman.

[Reprint Order No. 4904.]

Decomposition of hecogenin acetate toluene-*p*-sulphonylhydrazone with alkali gives little 3β-acetoxy-5α : 22a-spirost-11-en † (II); most of the steroid undergoes Wagner–Meerwein rearrangement, to give a small quantity of the known C-nor-D-homo-compound (V) and, as major product, a compound (A), which is considered to be (VII) or, less probably, (VI). These two rearranged products also arise from 3β-acetoxy-12β-methanesulphonyloxy-5α : 22a-spirostan (IV; R = Ac) by methanolysis. The structure of compound A is discussed in the light of both its reactions and the stereochemical requirements of the rearrangement.

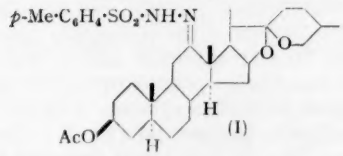
An attempt to prepare 5α : 22a-spirost-11-en-3-one (XVI) *via* 12α-hydroxy-5α : 22a-spirostan-3-one (XV; R = H) was unsuccessful, but 3β-acetoxy-5α : 22a-spirost-11-en (II) was readily obtained by the action of zinc upon 3β-acetoxy-12α : 23-dibromo-5α : 22a-spirostan-11β-ol (XIX). The structure of (II) was proved by its conversion, *via* the 11α : 12α-epoxide, into 3β : 12α-diacetoxy-5α : 22a-spirostan (XII; R = Ac).

The use of Δ^{11}-compounds derived from bile acids as intermediates in the partial synthesis of 11-keto-steroids is well known (see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd Ed., pp. 452 *et seq.*), but the method has not been applied in the steroid sapogenin series, possibly for lack of a convenient method of preparing the Δ^{11}-compounds. Bamford and Stevens (*J.*, 1952, 4735) have, however, recently shown that the toluene-*p*-sulphonylhydrazones of aliphatic and alicyclic ketones can be converted into olefins by treatment with alkali:

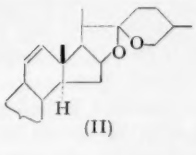
$$R{\cdot}CH_2{\cdot}CR'{:}N{\cdot}NHTos \xrightarrow{NaOH} R{\cdot}CH{:}CHR' + N_2 + TosONa \quad (Tos = p\text{-}C_6H_4Me{\cdot}SO_2)$$

the reaction is sometimes attended by rearrangement of the carbon skeleton (see below). This observation opened a possible route from hecogenin to 3β-acetoxy-5α : 22a-spirost-11-en (II) and hence to 11-oxotigogenin acetate; methods are already known for the conversion of the last-mentioned compound into cortisone.

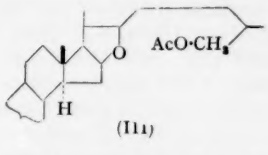
Hecogenin acetate reacted with toluene-*p*-sulphonhydrazide very slowly in boiling ethanol, but much faster in the presence of hydrochloric acid or in glacial acetic acid. Treatment of



(I)



(II)



(III)

the resulting toluene-*p*-sulphonylhydrazone (I) with caustic alkali in diethylene glycol at 130—140° or in boiling *n*-butanol or *n*-propanol produced mixtures from which three pure compounds were isolated. These compounds, which will be called A, B, and C (these letters refer to the acetates, unless otherwise specified), were obtained in yields of 50—55, <5, and up to 25% respectively.

Compound A had the correct elementary analysis for the required Δ^{11}-compound (II),

* Part VII, *J.*, 1954, 747.

† Scheer, Kostic, and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 4871) have shown that sarsasapogenin and smilagenin differ in their configurations at $C_{(25)}$ and possibly not, as earlier thought, at $C_{(22)}$. Although this finding casts some doubt on the nature of the isomerism of other sapogenins, we propose, in the absence of definite information on this point, to use the conventional name "22a-spirostan" for compounds derived from hecogenin. James (*Chem. and Ind.*, 1953, 1388) has very recently shown that hecogenin and smilagenin have the same configuration at $C_{(25)}$.

and its rotation (−57°) agreed with that (−66°) calculated from the rotation of tigogenin acetate and the contribution of an 11 : 12-double bond. The presence of a double bond was shown by the tetranitromethane test and by the formation of a very unstable crystalline dibromide. Doubt was cast upon structure (II) for compound A when an attempt was made to obtain tigogenin acetate from it by hydrogenation in presence of Adams catalyst. After 1 mol. of hydrogen had been taken up, the product was seen, from its infra-red absorption, to have undergone partial disruption of the side-chain. An attempt to complete this process by carrying the reduction to a total uptake of 2 mols. of hydrogen gave a mixture from which no pure compound could be isolated, whereas tigogenin acetate readily yielded 3β : 26-diacetoxy-5α : 22a-furostan (III) by reduction under similar conditions and subsequent acetylation.

Compound A reacted readily with 1 mol. of monoperphthalic acid to give two isomeric compounds, which from their analyses and infra-red spectra appeared to be epoxides. These two, " epoxide P " and " epoxide Q," were isolated in a ratio of *ca.* 1 : 2. If these had been isomeric 11 : 12-epoxides derived from (II), then lithium aluminium hydride should have converted one of them (the 11α : 12α-epoxide) into 12α-hydroxytigogenin and the other (11β : 12β-epoxide) into 11β-hydroxytigogenin (cf. Barton, *J.*, 1953, 1027; Fürst and Scotoni, *Helv. Chim. Acta*, 1953, **36**, 1332, 1410). Both epoxides were rather resistant to reduction with lithium aluminium hydride, but under sufficiently vigorous conditions gave diols which with pyridine and acetic anhydride at 100° yielded only monoacetates. The failure of the newly formed hydroxy-groups to undergo acetylation showed that neither of the diols was 12α-hydroxytigogenin and the physical properties of both monoacetates differed from those of the known 11β-hydroxytigogenin 3-monoacetate (Djerassi, Batres, Velasco, and Rosenkranz, *J. Amer. Chem. Soc.*, 1952, **74**, 1712). Further, the diol monoacetates were oxidised only slowly by chromic acid and the sole isolatable product, in each instance, was unchanged starting material.

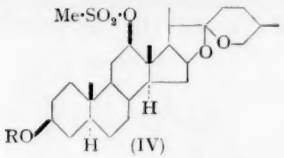
These experiments not only showed that the epoxides were not those derived from (II) but also suggested strongly that the double bond in compound A was ditertiary, since reduction with lithium aluminium hydride of the isomeric epoxides derived from such a compound would give isomeric (but not epimeric) tertiary alcohols (cf. Barton, *loc. cit.*). This was supported by the fact that the triol resulting from the action of osmium tetroxide upon compound A yielded only a monoacetate with acetic anhydride and pyridine at 100°.

In order to accommodate a ditertiary double bond in compound A, it is necessary to postulate a rearrangement of the carbon skeleton during decomposition of (I), if extremely improbable double bond shifts are excluded. Now it has already been mentioned that such rearrangements are liable to occur; camphor toluene-*p*-sulphonylhydrazone, for example, undergoes Wagner–Meerwein rearrangement during decomposition with alkali and gives camphene (Bamford and Stevens, *loc. cit.*); further, Hirschmann, Snoddy, and Wendler (*J. Amer. Chem. Soc.*, 1952, **74**, 2693) have shown that solvolysis of the rockogenin derivative (IV; R = $MeO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO$) was accompanied by rearrangement and yielded a product that they formulated as (V).* This compound was clearly a possible product of our reaction, and in fact, the minor product B had physical properties agreeing with those quoted for (V; R = Ac). In order to obtain an authentic specimen of (V; R = Ac), 3β-acetoxy-12β-methanesulphonyloxy-5α : 22a-spirostan (IV; R = Ac) was prepared by reduction of hecogenin acetate with sodium borohydride and treatment of the product with methanesulphonyl chloride in pyridine. When the crude (IV; R = Ac), which contained some of the 12α-epimer, was boiled in methanol and the product reacetylated, the major product was compound A, the expected (V; R = Ac) being isolated in very small quantity. (The 12α-methanesulphonyloxy-compound was recovered unchanged : it was found to be stable to prolonged boiling with methanol and was recovered after alkaline hydrolysis and re-acetylation of the amorphous 3-hydroxy-compound; cf. Hirschmann *et al.*, *loc. cit.*).

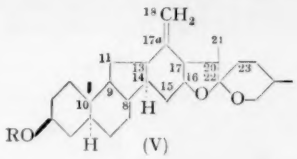
It is known that the Wagner–Meerwein rearrangement occurs most readily (or, in some

* We refrain from naming this ring system at present but, if essential, names of the type 3β-hydroxy-c nor-D-homo-5α : 22a-spirost-17a-en (for V, R = H) would be used, with numbering as shown for (V) (cf. Fried and Klingsberg, *J. Amer. Chem. Soc.*, 1953, **75**, 4929; Hiskey, Hirschmann, and Wendler, *ibid.*, p. 5135). No assumptions are at present made about the stereochemistry at $C_{(13)}$.

instances, only) when the four reacting centres lie in a plane (cf. Barton, *loc. cit.*). In (IV) the $C_{(12)}$–O bond is β-orientated (equatorial) and the condition of co-planarity is satisfied by the chains $O–C_{(12)}–C_{(13)}–C_{(14)}$ and $O–C_{(12)}–C_{(11)}–C_{(9)}$; in the 12α-epimer (polar) of (IV) there are no similar sets of co-planar centres and, as Hirschmann *et al.* (*loc. cit.*) have shown and we have confirmed, the 12α-methanesulphonyloxy-compounds are not affected by the conditions causing rearrangement in (IV). (Analogous compounds in the bile acid series are known to undergo simple elimination under more vigorous conditions with formation of an 11 : 12-double bond; the co-planar atoms in this instance are $O–C_{(12)}–C_{(11)}–11β$-H.)



(IV)



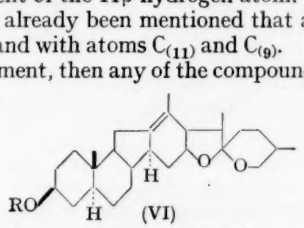
(V)

In the decomposition of (I), it is probable that a double-bond rearrangement of the following type occurs under the influence of base and that it is the azo-form (which may well exist only transitorily) that undergoes decomposition and rearrangement through the conventional carbonium-ion intermediates (cf. Wheland, " Advanced Organic Chemistry," John Wiley & Sons, Inc., New York, 2nd Ed.; Ingold, *J.*, 1953, 2845) :

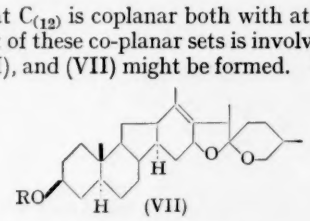
A double-bond migration of similar type is believed to occur during the Wolff–Kishner and related reactions; see Seibert, *Chem. Ber.*, 1947, **80**, 494; Todd, *J. Amer. Chem. Soc.*, 1949, **71**, 1356; Barton, Holness, and Klyne, *J.*, 1949, 2456; Beech, Turnbull, and Wilson, *J.*, 1952, 4686.

In such a double-bond rearrangement the newly formed single bond between $C_{(12)}$ and N will be predominantly in the more stable equatorial (*i.e.*, β-)configuration and the geometrical factors will be similar to those obtaining in (IV). The formation of some Δ^{11}-compound during the decomposition of (I) (see below) suggests that a proportion of the azo-intermediate has the $C_{(12)}$–N bond in the polar (α) configuration, which would be suitably disposed for involvement of the 11β-hydrogen atom.

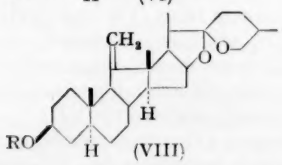
It has already been mentioned that a β-bond at $C_{(12)}$ is coplanar both with atoms $C_{(13)}$ and $C_{(14)}$ and with atoms $C_{(11)}$ and $C_{(9)}$. If the first of these co-planar sets is involved in the rearrangement, then any of the compounds (V), (VI), and (VII) might be formed. Formula



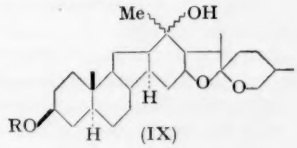
(VI)



(VII)



(VIII)

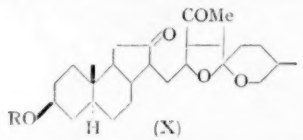


(IX)

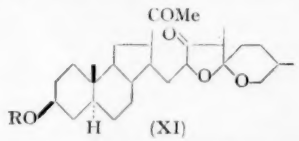
(V) has already been put forward for compound B (and the presence of an exocyclic methylene group was demonstrated conclusively by Hirschmann *et al.*, *loc. cit.*), and either of the formulæ (VI) and (VII) would account for the properties of compound A. On the other hand, rearrangement involving the second of the above sets of coplanar atoms could

give rise only to structure (VIII), which would account for the properties neither of compound A nor of compound B. [Compound B is not to be represented by formula (VIII), because the ketone derived from it by cleavage of the exocyclic double bond shows a peak in the infra-red at 1712 cm.$^{-1}$ (Hirschmann *et al.*, *loc. cit.*), whereas (VIII) would give a 5-membered ring ketone with carbonyl absorption at *ca.* 1740 cm.$^{-1}$.] A further argument against this second mode of rearrangement is that it would involve a primary carbonium ion, which would be less favoured, on grounds of stability, than the tertiary carbonium ion involved in the alternative scheme.

We consider, therefore, in agreement with the American workers, that compound B has formula (V) and, further, that compound A is either (VI) or (VII). An attempt to obtain



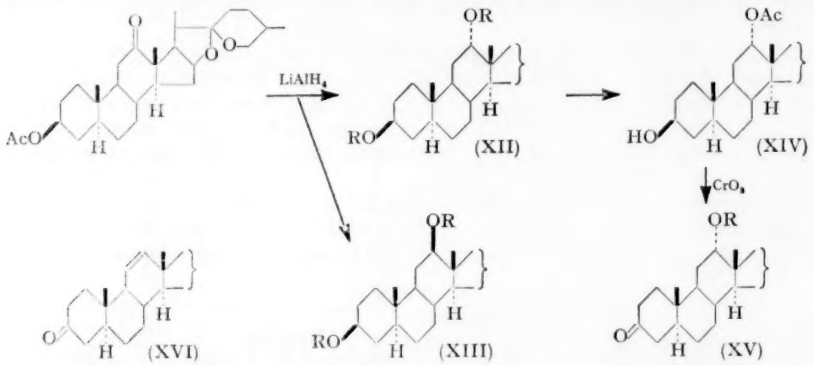
(X)



(XI)

direct evidence of such a close inter-relation was, unfortunately, inconclusive. Whether compound A has structure (VI) or (VII), one of the two isomeric epoxides, P and Q, should, on reduction with lithium aluminium hydride, give the tertiary alcohol (IX), and this might, in turn, be expected to yield (V) on dehydration. However, phosphorus oxychloride treatment, in cold pyridine, of the monoacetate of either diol resulting from reduction of the epoxides P and Q yielded only compound A, and infra-red analysis showed that (V) was not formed in significant amount.

The available evidence is insufficient to allow a clear choice between structures (VI) and (VII), but some support for structure (VII) comes from results of periodate fission of the triol obtained from compound A with osmium tetroxide. The product of this reaction was a diketone, which was shown by the nitroprusside test to be a methyl ketone; its infra-red spectrum showed bands at 1714 cm.$^{-1}$, corresponding to a normal ketone, and at 1740 cm.$^{-1}$,



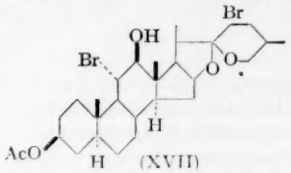
corresponding to a 5-membered ring ketone. These results would agree with either of the postulated structures for compound A, since the products from (VI) and (VII) would be (X) and (XI) respectively. However, compound (XI), which is a potential α-ketol, might be expected to show reducing properties, whereas there is no obvious reason why (X) should do so. In fact, the diketone did give a weak positive test with Fehling's solution, suggesting that it had structure (XI) and that compound A is to be represented by (VII).

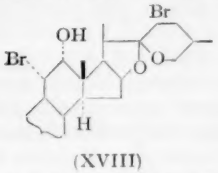
Along with the work described above, the synthesis of Δ^{11}-compounds by unambiguous methods was investigated. First, an attempt was made to prepare 5α : 22a-spirost-11-en-3-one (XVI) by the method shown, for comparison with the product of chromic oxidation of compound A (free alcohol).

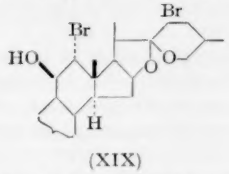
Hecogenin acetate was reduced with lithium aluminium hydride (Hirschmann *et al.*, *loc. cit.*) and, after acetylation, the rockogenin diacetate (XIII; R = Ac) was separated from

its 12α-epimer (XII; R = Ac) by chromatography. The 12α-acetoxy-compound (XII; R = Ac), on treatment with potassium hydrogen carbonate in boiling aqueous methanol, gave the 12-monoacetate (XIV) (12α-acetoxy-groups are known to be rather resistant to hydrolysis; see Koechlin and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 918), and oxidation of the latter compound with chromic acid gave the 3-keto-steroid (XV; R = Ac). Both the free alcohol (XV; R = H) and the benzoate (XV; R = Bz) were prepared and heated under water-pump pressure, but each compound sublimed unchanged. Lack of material prevented further investigation of the reaction.

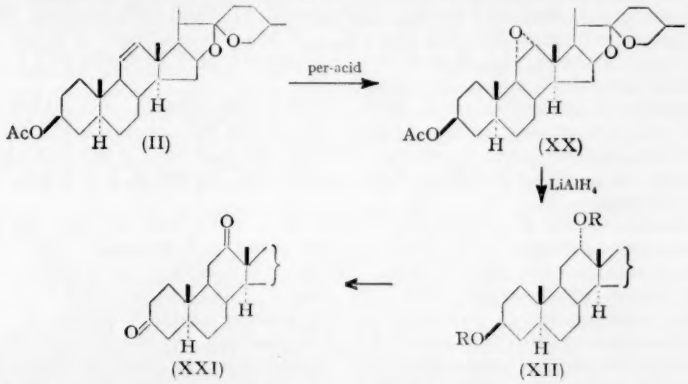
Cornforth and Osbond (*Chem. and Ind.*, 1953, 919) have shown that the mixture of bromohydrins (XVII) and XVIII), obtained by reduction of 11α : 23-dibromohecogenin


(XVII)


(XVIII)


(XIX)

acetate with sodium borohydride, is reduced with zinc in acetic acid to a compound formulated as 3β-acetoxy-23-bromo-5α : 22a-spirost-11-en, but we have found some difficulty in obtaining the pure bromine-free compound (II) by this reaction under more vigorous conditions. It seemed probable that this elimination reaction would proceed most readily if both the bromine and the hydroxy-groups were polar (cf. Barton and Rosenfelder, *J.*, 1951, 1048; Barton, *Experientia*, 1950, **6**, 316) as in the bromohydrin (XIX) (Cornforth and Osbond, *loc. cit.*) and, in fact, (XIX) reacted with zinc in boiling acetic acid to give, in high yield, a compound with the correct analysis for 3β-acetoxy-5α : 22a-spirost-11-en (II). There was initially some doubt about the structure of the reduction product, since it gave only a very weak tetranitromethane test, but it was proved to be (II) by the following



reactions. With monoperphthalic acid it gave a single compound, which, by analogy with the epoxidation of Δ^{11}-compounds in the bile acid series, must be the 11α : 12α-epoxide (XX) (Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 495; McKenzie, McGuckin, and Kendall, *ibid.*, p. 555; Press and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 878; Berner and Reichstein, *ibid.*, 1946, **29**, 1374). Vigorous reduction of the epoxide with lithium aluminium hydride in boiling tetrahydrofuran gave 5α : 22a-spirostan-3β : 12α-diol (XII; R = H), which was characterized as its diacetate and by chromic oxidation to hecogenone (XXI).

With the synthesis of (II), the structure of the third product formed from (I) by decomposition with alkali became clear, since compound C was found, by comparison of its physical properties and infra-red spectrum with those of an authentic specimen, to be the desired Δ^{11}-compound (II). The yield of this compound from (I) was, however, too low for the method to be of any interest in a practicable synthesis of cortisone.

Addendum.—Since this manuscript was prepared, Hiskey, Hirschmann, and Wendler (*J. Amer. Chem. Soc.*, 1953, **75**, 5135) have briefly reported both the preparation of compound A from hecogenin toluene-*p*-sulphonylhydrazone and the oxidation of the olefin with osmium tetroxide. They assign to compound A the alternative structures (VI) and (VII) and show that it can be obtained from (V) by treatment with formic acid at room temperature; this observation supports the relation between compounds A and B that we have put forward.

In view of this ready conversion of compound B into compound A with acid, it seemed possible that our failure to obtain B in significant quantity by methanolysis of (IV; R = Ac) was a consequence of double-bond migration induced by acid present in the crude (IV) employed or by the methanesulphonic acid liberated during the reaction. We have now found that, if (IV; R = Ac) is treated with potassium *tert.*-butoxide in *tert.*-butanol, a high yield of B is, in fact, obtained, but, surprisingly, compound B was not affected by treatment either with methanesulphonyl chloride or with toluene-*p*-sulphonic acid in boiling chloroform–methanol. Subsequent experiments confirmed that the nature of the solvent is more important in determining the yield of B than is the presence or absence of base.

Experimental

Rotations were determined on chloroform solutions (*ca.* 1%) unless otherwise stated. M. p.s were taken on a Kofler block. A Perkin–Elmer model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra.

Hecogenin Acetate Toluene-p-*sulphonylhydrazone* (I).—(*a*) Hecogenin acetate (100 g.), toluene-*p*-sulphonhydrazide (100 g.), and anhydrous ethanol (7 l.) were boiled together under reflux for 65 hr. The mixture was allowed to cool somewhat and the solid (100 g., 74%) was then filtered off, washed with a little ethanol, and dried. This material, which melted at 268—269°, was suitable for use in the next stage. Crystallisation from a mixture of ethanol and chloroform gave the *hydrazone* as fine needles, m. p. 274° (decomp.), $[\alpha]_D$ −15° (Found: C, 67·1; H, 8·1; N, 4·5; S, 5·0. $C_{36}H_{52}O_6N_2S$ requires C, 67·5; H, 8·2; N, 4·4; S, 5·0%), $\lambda_{max.}$ (in EtOH) 226 mμ (ε = 11,600), ν_{max} (in CS_2) 3250 (imine), 1732 and 1245 (acetate), 1342 and 1160 (monosubstituted sulphonamide), 977, 914, 897, and 860 (22a-spirostan) (C.S. no. 112).*

In another experiment, with 36 g. of hecogenin acetate, 18·6, 24·9, and 31·1 g. of derivative were deposited after 6, 24, and 50 hr. respectively.

(*b*) A solution of hecogenin acetate (20 g.) in chloroform (150 ml.) was added to toluene-*p*-sulphonhydrazide (10 g.) in a mixture of ethanol (200 ml.) and concentrated hydrochloric acid (5 ml.); crystalline solid began to separate within a few minutes. After being left overnight the hydrazone (23 g., 85%) was filtered off, washed with methanol, and dried; it had m. p. 278—280° (decomp.).

(*c*) Hecogenin acetate (2 g.) was dissolved in warm acetic acid (60 ml.), the solution was cooled, and toluene-*p*-sulphonhydrazide (2 g.) was added with shaking. After about 5 min., solid began to separate, and after an hour this solid was filtered off and washed with ethanol. The product (2·4 g., 89%) melted at 264—265° (decomp.) and had $[\alpha]_D$ −14·9°.

Alkaline Decomposition of Hecogenin Acetate Toluene-p-*sulphonylhydrazone.*—(*a*) Sodium (15 g.) was dissolved in diethylene glycol (1 l.) with warming, the solution was cooled to about 50°, and the hydrazone (50 g.) was added. The mixture was then heated gradually to 130—140° and kept at that temperature until no further gas evolution was apparent. After being cooled to about 60°, the mixture was diluted with much water and kept overnight at room temperature. The solid was filtered off, washed with water, and dried in a desiccator. This crude product (35 g.), which had no definite m. p., was crystallised twice from boiling acetonitrile. The resulting "compound A" (free alcohol) (21·4 g.), which appeared to be solvated, melted indefinitely between 125° and 133° after preliminary softening. This material was acetylated on the water-bath for 30 min. with acetic anhydride (215 ml.) and pyridine (215 ml.). The solution was evaporated to dryness, the remaining acetic anhydride was removed by repeated evaporation with methanol, and the residue was crystallised from methanol. The "compound A" (19·5 g., 55%), so obtained, melted at 141—144°. Further crystallisation from aqueous methanol gave material melting at 142—145°, $[\alpha]_D$ −57° (Found: C, 76·55; H, 9·65. Calc. for

* Infra-red spectra thus marked have been deposited with the Society. Photo-copies (price, 3*s.* 0*d.* each per copy) can be obtained on application, quoting the C.S. no., to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

$C_{29}H_{44}O_4$: C, 76·3; H, 9·7%), $\nu_{max.}$ (in CS_2) 1733 and 1238 (acetate), 980, 920, 898 and 860 (22a-spirostan). Hiskey *et al.* (*loc. cit.*) give m. p. 142—144°, $[\alpha]_D$ —52·6° in $CHCl_3$.

The free *alcohol*, prepared as above, or by hydrolysis of the acetate with alcoholic potassium hydroxide, had m. p. 120—125° and $[\alpha]_D$ −55° (Found, after drying at 100°/0·01 mm.: C, 78·4; H, 10·25. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%), $\nu_{max.}$ (in Nujol) 3400 (hydroxyl), 983, 920, 898, and 865 cm.$^{-1}$ (22a-spirostan).

The acetonitrile mother-liquors from the first crystallisation of the crude decomposition product were evaporated to dryness and the residue crystallised from methanol. The solid (1·2 g.) which separated was acetylated with acetic anhydride (20 ml.) and pyridine (20 ml.) on the water-bath for 30 min. The product (0·94 g.), isolated in the usual way, melted at 206—211° after crystallisation from light petroleum (b. p. 60—80°). Its infra-red spectrum was identical with that of 3β-acetoxy-5α : 22a-spirost-11-en (II) (p. 1748) and there was no m. p. depression when samples were mixed.

An alternative method of isolating compound A involved acetylation of the crude reaction product followed by chromatography of the mixed acetates. The product, however, still required repeated crystallisation before it was quite pure and the yield was rather low.

(*b*) Sodium (3 g.) was dissolved in *n*-butanol (800 ml.), the hydrazone (28 g.) was added, and the solution was boiled under reflux for 30 min. The solvent was removed by steam-distillation and the solid which separated was fractionally crystallised from methanol, to give compound A (free alcohol) (9·18 g., 51%), m. p. 110—125°, and 5α : 22a-spirost-11-en-3β-ol (II; 3-HO in place of 3-AcO) (2·1 g., 12%), which crystallised from methanol–methylene chloride in tablets, m. p. 192—194°, $[\alpha]_D$ −37°. [The acetate (II), prepared in the usual way, crystallised from light petroleum in prisms, m. p. 204—208°, $[\alpha]_D$ −43°.]

The solid obtained from the combined mother-liquors from the methanol crystallisations was acetylated and crystallised from light petroleum, to yield 3β-acetoxy-5α : 22a-spirost-11-en (II) [2·6 g.; total yield of (II), 25%], m. p. 204—206°. The mother-liquors from this crystallisation yielded a solid which was chromatographed on alumina (150 g.), giving (V; R = Ac) (700 mg., 3·5%), m. p. 215°, $[\alpha]_D$ −81°. Hirschmann *et al.* (*loc. cit.*) give m. p. 221—225°, $[\alpha]_D$ −80·6° in $CHCl_3$.

Reaction of Compound A with Bromine.—Compound A (0·912 g.) in carbon tetrachloride (40 ml.) was cooled to −25° and treated with bromine (320 mg.) in carbon tetrachloride (2 ml.). The bromine colour was discharged within about 1 min. and a little hydrogen bromide was evolved. The solution was allowed to come to 0°, and was then washed successively with water, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a gum which crystallised on trituration with methanol. The *dibromide* (0·81 g., 66%) was filtered off, washed with a little methanol, and dried. It melted at 108° (decomp.) and had $[\alpha]_D$ −33° (Found: Br, 25·1. $C_{29}H_{44}O_4Br_2$ requires Br, 25·9%), $\nu_{max.}$ (in CS_2) 1735 and 1240 (acetate), 988, 918, 898 and 860 (22a-spirostan) and 702 cm.$^{-1}$ (bromide) (C.S. no. 113). The compound decomposed when kept at room temperature or on attempted crystallisation.

3β : 26-*Diacetoxy*-5α : 22a-*furostan* (III).—Tigogenin acetate (0·5 g.) in acetic acid (25 ml.) was hydrogenated in the presence of Adams catalyst (200 mg.) at room temperature and pressure. After about 24 hr., 1 mol. of hydrogen had been taken up; the catalyst was then filtered off, and the filtrate evaporated to dryness under reduced pressure. The residue was acetylated on the steam-bath for 30 min. with acetic anhydride (10 ml.) and pyridine (10 ml.). The solvents were removed under reduced pressure and the residue crystallised from methanol, to give unchanged tigogenin acetate as needles (0·11 g.), m. p. 204—207°, $[\alpha]_D$ −72°. Dilution of the mother-liquors with water yielded the furostan, which crystallised from aqueous methanol as fine needles (0·2 g.), m. p. 114—116°, $[\alpha]_D$ −14°, $\nu_{max.}$ (in CS_2) 1732 and 1240 cm.$^{-1}$ (acetate). The bands characteristic of the 22a-spirostan system were almost absent. Doukas and Fontaine (*J. Amer. Chem. Soc.*, 1951, **73**, 5917) give m. p. 116—117° and $[\alpha]_D$ −15° in $CHCl_3$.

The free diol, prepared from the diacetate by hydrolysis with ethanolic potassium hydroxide, crystallised in needles, m. p. 165—167°, $[\alpha]_D$ −6°, $\nu_{max.}$ (in Nujol) 3300 cm.$^{-1}$ (hydroxyl). The spirostan bands were absent. Doukas and Fontaine (*loc. cit.*) give m. p. 163—166°, $[\alpha]_D$ −4° in $CHCl_3$.

Epoxidation of Compound A.—Compound A (5 g.) in chloroform (200 ml.) was treated at room temperature with ethereal monoperphthalic acid (2·8N; 15 ml.). After being left for 30 min. at room temperature, the mixture was washed three times with saturated aqueous sodium hydrogen carbonate, then with water, and was dried (Na_2SO_4). The solvent was removed and the residue, which rapidly crystallised, was chromatographed on alumina (Peter

Spence, Type H; 150 g.). Light petroleum–benzene (2 : 1) eluted epoxide P, and benzene and benzene–ether eluted epoxide Q. *Epoxide P* (1·06 g., 21%) melted at 189—190° after crystallisation from aqueous methanol and had $[\alpha]_D$ −66° (Found: C, 73·6; H, 9·3. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%), $\nu_{max.}$ (in CS_2) 1732 and 1240 (acetate), 980, 918, 895, and 860 cm.$^{-1}$ (22a-spirostan).

Epoxide Q (2·01 g., 39%) crystallised from aqueous methanol as colourless needles, m. p. 194—195°, $[\alpha]_D$ −63° (Found: C, 73·9; H, 9·4. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%), $\nu_{max.}$ (in CS_2) 1734 and 1240 (acetate), 980, 918, 895 and 860 (22a-spirostan). A mixture of the two epoxides melted between 140° and 160°. Their infra-red spectra were quite different in detail.

Reduction of Epoxide P.—Epoxide P (0·500 g.) in tetrahydrofuran (50 ml.) was boiled under reflux for 3·5 hr. with lithium aluminium hydride (0·5 g.). After decomposition of excess of hydride, the solution was poured into 0·5N-sulphuric acid (500 ml.) and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residual crystalline solid was heated on the water-bath for 30 min. with acetic anhydride (5 ml.) and pyridine (5 ml.). The solution was poured into water and extracted with ether, and the extract was washed successively with 0·5N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated to dryness. The crystalline residue (0·487 g.), on recrystallisation from methanol, deposited two forms of crystals, very large prisms, and feathery needles, which were easily separated mechanically. The prisms (0·383 g., 76%), consisting of *diol monoacetate*, melted at 192—194° and had $[\alpha]_D$ −63° (Found: C, 73·3; H, 9·5. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%). $\nu_{max.}$ (in CS_2) 3620 (hydroxyl), 1732 and 1240 (acetate), 978, 918, 898 and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 123). The needles (41 mg.) melted at 185—188°, undepressed on admixture with the starting epoxide.

Dehydration of Alcohol derived from Epoxide P.—The diol monoacetate described in the last paragraph (100 mg.) was treated in pyridine (2 ml.) with phosphorus oxychloride (0·5 ml.). After being left at room temperature for 2 hr., the mixture was poured on crushed ice, and the precipitated solid was filtered off, washed with water, and dried. Crystallisation from methanol gave material (51 mg.), m. p. 138°, undepressed on admixture with compound A. The infra-red spectra of the two samples were identical.

Reduction of Epoxide Q.—Epoxide Q (0·5 g.) in tetrahydrofuran (50 ml.) was reduced with lithium aluminium hydride (0·65 g.) for 5 hr. as described above for the isomer. The product was acetylated and worked up as above, giving, after crystallisation, first from methanol, then from light petroleum, the *diol monoacetate* as prisms (0·306 g., 61%), which melted at 161°, resolidified in needles, and melted finally at 170—171°; $[\alpha]_D$ −53° (*c*, 1·4 in $COMe_2$) (Found: C, 73·5; H, 9·75. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%), $\nu_{max.}$ (in CS_2) 3600 (hydroxyl), 1735 and 1240 (acetate), 980, 916, 897 and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 114).

Dehydration of Alcohol derived from Epoxide Q.—The foregoing diol monoacetate (0·155 g.) in pyridine (2 ml.) was treated with phosphorus oxychloride (0·5 ml.). After being left for 2 hr. at room temperature, the mixture was worked up in the usual way. Crystallisation of the gummy product from methanol gave compound A (0·092 g.), m. p. and mixed m. p. 138—143°.

Oxidation of Compound A with Osmium Tetroxide.—Compound A (1·6 g.) in dry ether (20 ml.) containing pyridine (0·7 ml.) was treated with osmium tetroxide (1·0 g.). The mixture, which began to deposit solid within a few minutes, was left at room temperature for *ca.* 65 hr. Ether was then removed under reduced pressure and the residue boiled under reflux with a solution of sodium sulphite (7·0 g.) in a mixture of ethanol (80 ml.) and water (40 ml.). After 4·5 hr., the solution was cooled and filtered and the residue extracted with boiling ethanol. The combined alcoholic solutions were evaporated to dryness under reduced pressure, the white gummy residue was dissolved in chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. This residue was acetylated overnight in acetic anhydride (70 ml.)–pyridine (70 ml.), finally being warmed on the steam-bath for 30 min. The mixture was evaporated to dryness under reduced pressure and the solid residue treated twice with methanol and distilled. The residual gum (1·65 g.) was crystallised from benzene–light petroleum (b. p. 60—80°), giving the triol monoacetate as rosettes of needles (1·18 g., 69%), m. p. 214—217°, $[\alpha]_D$ −40° (Found: C, 70·8; H, 9·4; Ac, 8·6. Calc. for $C_{29}H_{46}O_6$: C, 71·0; H, 9·45; Ac, 8·8%), $\nu_{max.}$ (in CS_2) 3620 (hydroxyl), 1732 and 1240 (acetate), 978, 918, 896, and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 115). Hiskey *et al.* (*loc. cit.*) give m. p. 215—218°, $[\alpha]_D$ −39·3° in $CHCl_3$.

The free *triol* was obtained by hydrolysis of the acetate with methanolic potassium hydroxide on the water-bath for 2 hr. The product crystallised from aqueous methanol in prisms, m. p. 229—233°, $[\alpha]_D$ −40° (Found: C, 72·1; H, 9·8. $C_{27}H_{44}O_5$ requires C, 72·3; H, 9·9%), $\nu_{max.}$ (in CS_2) 3350 (hydroxyl), 982, 918, 900, and 860 cm.$^{-1}$ (22a-spirostan).

Cleavage of the Triol with Periodic Acid.—The above triol (0·46 g.) in methanol (dried, and freshly distilled from 2 : 4-dinitrophenylhydrazine; 25 ml.) was treated with aqueous periodic acid (10%; 5 ml.). The mixture was left for 2 days at room temperature, water was added, and the flocculent precipitate was collected and crystallised from aqueous methanol. The *diketone* separated in needles (0·28 g., 61%), m. p. 157—160°, $[\alpha]_D$ −21° (Found: C, 72·7; H, 9·3. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%), $\nu_{max.}$ (in CS_2) 3620 (hydroxyl), 1740 and 1714 cm.$^{-1}$ (ketones). The band at 1740 cm.$^{-1}$, in the absence of one at *ca.* 1240 cm.$^{-1}$, is attributable to a strained ketone, *e.g.*, a ketone group in a 5-membered ring; the band at 1714 cm.$^{-1}$ is in the normal position for an unstrained ketone, as in an open-chain or 6-membered ring ketone. The compound gave a violet colour with sodium nitroprusside, showing the presence of a methyl ketone grouping, and gave some turbidity on being boiled with Fehling's solution.

Preparation and Methanolysis of 3β-*Acetoxy*-12β-*methanesulphonyloxy*-5α : 22a-*spirostan* (IV; R = Ac).—A solution of hecogenin acetate (10 g.) in ethanol (200 ml.) and methylene chloride (100 ml.) was treated with sodium borohydride (0·6 g.) in water (5 ml.). The mixture was kept for 3 days at room temperature and was then acidified, diluted with methylene chloride, and washed with water. The solvent was evaporated and the residue was crystallised repeatedly from methanol. The 3β-acetoxy-5α : 22a-spirostan-12β-ol (4·2 g., 42%), which melted at 211—216°, was contaminated with the 12α-hydroxy-compound (see below) (Found: C, 73·6; H, 9·7. Calc. for $C_{29}H_{46}O_5$: C, 73·4; H, 9·8%). Mueller, Norton, Stobaugh, Tsai, and Winniford (*J. Amer. Chem. Soc.*, 1953, **75**, 4892) give m. p. 218—220°.

The mixture (4 g.) was added to methanesulphonyl chloride (3 ml.) in pyridine (13 ml.) at 0°. After being left overnight at room temperature, the mixture was poured on ice and ether, and the organic layer was separated, washed successively with dilute hydrochloric acid and sodium carbonate solution, and dried. The residue left on evaporation was boiled under reflux for 2 hr. with methanol (100 ml.). The solution was evaporated to dryness and the residue was hydrolysed with a boiling 4% solution of potassium hydroxide in 80% ethanol for 30 min. The product, isolated with ether, was crystallised twice from methanol to yield compound A (free alcohol) (1·03 g.), m. p. 112°, $[\alpha]_D$ −52°. The acetate, prepared in the usual way, melted at 144—146° and had $[\alpha]_D$ −54°. The identity of this material with that prepared as described above was demonstrated by means of infra-red analysis and mixed m. p. determinations.

The mother-liquors from the crystallisation of compound A (free alcohol) were combined and evaporated and the residue was re-acetylated. The crude acetate was chromatographed on alumina (Peter Spence Grade H; 90 g.). Benzene eluted a further quantity of compound A (800 mg.), m. p. 144—146°, while benzene–chloroform eluted 3β-*acetoxy*-12α-*methanesulphonyloxy*-5α : 22a-*spirostan* (1·26 g.) which, after crystallisation from methanol, had m. p. 186—188°, $[\alpha]_D$ −21° (Found: C, 65·2; H, 8·7. $C_{30}H_{48}O_7S$ requires C, 65·2; H, 8·7%).

The mother-liquors from the crystallisations of the products from the chromatogram were combined and evaporated. Chromatography of the residue on alumina gave (V; R = Ac) (75 mg.), m. p. 215—216°, $[\alpha]_D$ −80° (Found: C, 75·9; H, 9·8. Calc. for $C_{29}H_{44}O_4$: C, 76·3; H, 9·7%).

Reduction of Hecogenin Acetate with Lithium Aluminium Hydride.—A suspension of hecogenin acetate (5·0 g.) in tetrahydrofuran (25 ml.) was added to lithium aluminium hydride (0·8 g.) in tetrahydrofuran (25 ml.), and the mixture was boiled under reflux for 1 hr. The solution was cooled, excess of hydride was decomposed by addition of ethyl acetate (15 ml.), and the mixture was poured on ice and 2N-sulphuric acid. The product was extracted into chloroform and the extract was dried and evaporated. The residue was treated on the water-bath for 1 hr. with acetic anhydride and pyridine. The solution was evaporated to dryness *in vacuo*, the residue triturated with methanol, and the solvent again evaporated under reduced pressure. The residue (5·31 g.) had $[\alpha]_D$ −52·7°.

The crude product was chromatographed on alumina (Peter Spence Grade H, acid-washed; Brockmann II—III; 150 g.). Benzene–light petroleum (1 : 4) eluted (*a*) crude 12α-acetoxy-compound, m. p. 80—135° (2·12 g.), and (*b*) crude 12β-acetoxy-compound, m. p. 164—176° (1·16 g.). The latter (1·76 g.), in much purer form (m. p. *ca.* 190°), was eluted completely by solvent mixtures ranging from benzene–light petroleum (1 : 2) through benzene to ether–benzene (1 : 9).

Fraction (*a*) from the first column was again chromatographed on alumina (150 g.). Benzene–light petroleum (1 : 4 and 1 : 2) eluted the 12α-acetoxy-compound (0·562 g.), m. p. 145—151°. Further elution with benzene–light petroleum gave a mixed fraction; benzene and ether–benzene (1 : 9) eluted the 12β-acetoxy-compound (0·700 g.), m. p. *ca.* 195°.

3β : 12α-Diacetoxy-5α : 22a-spirostan (XII; R = Ac) (yield 10%) crystallised from aqueous

methanol in prisms, m. p. 153—156°, $[\alpha]_D$ −17° (*c*, 1 in $CHCl_3$), −15° (in $COMe_2$), $\nu_{max.}$ (in CS_2) 1738 and 1240 (acetate), 976, 918, 895, and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 124). Hirschmann *et al.* (*loc. cit.*) give m. p. 156—159°, $[\alpha]_D$ −15° in acetone.

The free diol (XII; R = H), obtained by hydrolysis of the diacetate with ethanolic potassium hydroxide, melted at 200—206° and had $[\alpha]_D$ −30° (in acetone), $\nu_{max.}$ (in Nujol) 3600 and 3450 (hydroxyl) and 981, 919, 903 and 863 cm.$^{-1}$ (22a-spirostan). Hirschmann *et al.* (*loc. cit.*) give m. p. 216—220°, $[\alpha]_D$ −32·4° in acetone.

3β : 12β-Diacetoxy-5α : 22a-spirostan (rockogenin diacetate) (XIII; R = Ac) (yield 45%) melted at 198—203° after crystallisation from methanol, and had $[\alpha]_D$ −68° (*c*, 1 in $CHCl_3$), −63° (in acetone), $\nu_{max.}$ (in CS_2) 1735 and 1240 (acetate), 978, 918, 898, and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 116). Hirschmann *et al.*, *loc. cit.*) give m. p. 202—206·5°, $[\alpha]_D$ −65·1° in acetone.

The free diol (XIII; R = H) melted at 216—219° and had $[\alpha]_D$ −60° (in acetone), $\nu_{max.}$ (in Nujol) 3300 (hydroxyl) and 973, 914, 892, and 860 cm.$^{-1}$ (22a-spirostan). Hirschmann *et al.* (*loc. cit.*) give m. p. 218·5—220·5°, $[\alpha]_D$ —63·8° in acetone.

12α-*Acetoxy*-5α : 22a-*spirostan*-3β-*ol* (XIV).—3β : 12α-Diacetoxy-5α : 22a-spirostan (0·750 g.) was boiled under reflux for 2 hr. with potassium hydrogen carbonate (0·225 g.) in methanol (24 ml.) and water (6 ml.). The crystalline solid (585 mg., 85%) which had separated was collected by filtration and used as such in the next stage. A portion, crystallised twice from ethanol, gave the *diol monoacetate* with m. p. 231—233° and $[\alpha]_D$ −15° (Found: C, 73·4; H, 9·5. $C_{29}H_{46}O_5$ requires C, 73·4; H, 9·8%), $\nu_{max.}$ (in CS_2) 3620 (hydroxyl), 1739 and 1240 (acetate), 978, 920, 898, and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 117).

12α-*Acetoxy*-5α : 22a-*spirostan*-3-*one* (XV; R = Ac).—The foregoing monoacetate (0·55 g.) in glacial acetic acid (15 ml.) was treated with chromic anhydride (1·5 equiv.) and left at room temperature for 4 hr. Excess of chromic anhydride was destroyed with methanol, some of the solvent was removed, and the residue was diluted with water. The *ketone* (0·50 g., 91%), crystallised from aqueous ethanol, had m. p. 214—217°, $[\alpha]_D$ +1° (Found: C, 73·6; H, 9·4. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%), $\nu_{max.}$ (in CS_2) 1739 and 1237 (acetate), 1715 (ketone), 981, 920, 899, and 863 cm.$^{-1}$ (22a-spirostan) (C.S. no. 118).

The free *alcohol* (XV; R = H), obtained from the acetate with methanolic potassium hydroxide, melted at 254—257° after crystallisation from aqueous alcohol and had $[\alpha]_D$ −30° (Found: C, 75·6; H, 9·8. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%), $\nu_{max.}$ (in CS_2) 3620 (hydroxyl), 1712 (ketone), 979, 917, and 895 cm.$^{-1}$ (22a-spirostan).

Oxidation of Compound A (Free Alcohol) with Chromic Anhydride.—The alcohol (1·0 g.) in glacial acetic acid (15 ml.) was treated with chromic anhydride in acetic acid (0·55N; 17 ml.), and the mixture was left at room temperature for 4 hr. Excess of chromic anhydride was destroyed with methanol, and the product was worked up in the usual way. The *ketone* melted at 101—104° and had $[\alpha]_D$ −40° (Found: C, 78·3; H, 9·8. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·8%), $\nu_{max.}$ (in CS_2) 1715 (ketone), 980, 920, 900, and 860 cm.$^{-1}$ (22a-spirostan). The 2 : 4-*dinitrophenylhydrazone* was an orange compound, m. p. 206—208° (Found: N, 9·8. $C_{33}H_{44}O_6N_4$ requires N, 9·5%).

3β-*Acetoxy*-5α : 22a-*spirost*-11-*en* (II).—3β-Acetoxy-12α : 23-dibromo-5α : 22a-spirostan-11β-ol (Cornforth and Osbond, *loc. cit.*) (3·0 g.) was boiled under reflux for 3·5 hr. with stirring with zinc dust (acid-washed; 30 g.) and glacial acetic acid (300 ml.). The hot solution was filtered, the solid washed with hot acetic acid, and the combined filtrate and washings were evaporated to small bulk and diluted with water. The *product* (2·05 g.; m. p. 187—200°) was crystallised from acetone, to give prisms (1·41 g.), m. p. 202—205° and a second crop (0·27 g.) with slightly lower m. p. (total yield 78%). Further crystallisation from acetone raised the m. p. to 206—210°; $[\alpha]_D$ was −44° (Found: C, 76·3; H, 9·65. $C_{29}H_{44}O_4$ requires C, 76·3; H, 9·7%). $\nu_{max.}$ (in CS_2) were 1732 and 1240 (acetate), 978, 918, 895, and 860 cm.$^{-1}$ (22a-spirostan). Strong maxima at 703 and 760 cm.$^{-1}$ suggest the presence of a *cis*-1 : 2-disubstituted ethylene grouping; this is supported by a shoulder (at 3000 cm.$^{-1}$) on the strong C–H stretching band at 2950 cm.$^{-1}$ (cf. Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1) (C.S. no. 119).

The same Δ^{11}-compound was obtained by a similar method from 3β-acetoxy-23-bromo-11β : 12β-epoxy-5α : 22a-spirostan (Cornforth and Osbond, *loc. cit.*). The yield in this case was only about 30%.

The free *alcohol*, obtained by hydrolysis of the acetate with ethanolic sodium hydroxide, was a solvate, m. p. 184—188° after crystallisation from methanol. After being dried at 120°/0·1 mm., it melted at 193—195° and had $[\alpha]_D$ −36° (Found: C, 77·8; H, 10·2. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%), $\nu_{max.}$ (in Nujol) 3560 and 3330 (hydroxyl), 978, 918, 900, and 861 cm.$^{-1}$ (22a-spirostan). This compound, like the acetate, showed bands of medium intensity at 702 and

760 cm.$^{-1}$ and a shoulder at 3000 cm.$^{-1}$, indicative of the presence of a *cis*-1 : 2-disubstituted ethylene grouping.

3β-*Acetoxy*-11α : 12α-*epoxy*-5α : 22a-*spirostan* (XX).—3β-Acetoxy-5α : 22a-spirost-11-en (200 mg.) in chloroform (6 ml.) was treated with ethereal monoperphthalic acid (2·8N; 0·5 ml.). After being left overnight in the refrigerator, the solution was washed consecutively with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness. The residual white solid was crystallised from aqueous acetone, to yield the *epoxide* as needles (155 mg., 75%), m. p. 221—225°, $[\alpha]_D$ −49·5° (Found: C, 73·4; H, 9·3. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%), $\nu_{max.}$ (in CS_2) 1735 and 1240 cm.$^{-1}$ (acetate), 978, 918, 895, and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 120). There was no indication of the presence of the isomeric 11β : 12β-epoxide.

5α : 22a-*Spirostan*-3β : 12α-*diol* (XII; R = H).—The foregoing epoxide (0·5 g.) was boiled under reflux for 2 hr. with a solution of lithium aluminium hydride (0·6 g.) in tetrahydrofuran (25 ml.). The excess of hydride was destroyed and the product isolated in the usual way. Crystallisation of the crude diol (0·5 g.) from methanol gave material with m. p. 207—214°, $[\alpha]_D$ −30° (*c*, 1·05 in $COMe_2$). The m. p. of a mixture of this material and a sample of (XII; R = H) prepared as described on p. 1748 was not depressed; the infra-red spectra of the specimens were identical.

The diacetate (XII; R = Ac), obtained from the crude diol with pyridine–acetic anhydride on the water-bath, melted at 153—155° after crystallisation from aqueous methanol and had $[\alpha]_D$ −14° (*c*, 1·0 in $COMe_2$). The m. p. of a mixture of this material with an authentic sample was undepressed and the infra-red spectra were identical. The diacetate was obtained in 44% yield from epoxide.

Hecogenone (XXI).—The crude 3β : 12α-diol prepared as described above (200 mg.) in acetic acid (7 ml.) was treated with 0·55N-solution of chromic anhydride in acetic acid (5·5 ml.). The solution was left at room temperature for 4 hr., excess of chromic anhydride was destroyed with methanol, and the product poured into water. Crystallisation from methanol gave hecogenone as plates, m. p. 232—235°, $[\alpha]_D$ +21°, $\nu_{max.}$ (in CS_2) 1710 (ketone), 978, 918, 896 and 860 cm.$^{-1}$ (22a-spirostan) (C.S. no. 121). The material was identical with a sample prepared from rockogenin by the same method. Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruof (*J. Amer. Chem. Soc.*, 1947, **69**, 2167) give m. p. 237—240°.

Solvolysis of 3β-*Acetoxy*-12β-*methanesulphonyloxy*-5α : 22a-*spirostan in Presence of Base. Compound* (V).—Rockogenin 3-monoacetate was prepared as described above, and was chromatographed on acid-washed alumina (Brockmann II—III). The material eluted with benzene was crystallised from methanol and then had m. p. 214—219°, $[\alpha]_D$ −65° (in $CHCl_3$), −61° (in dioxan), $\nu_{max.}$ 3620 (hydroxyl), 1736 and 1238 (acetate), 978, 918, 895, and 862 (22a-spirostan) in CS_2 (C.S. no. 122). Mueller, Norton, Stobaugh, Tsai, and Winniford (*J. Amer. Chem. Soc.*, 1953, **75**, 4892) give m. p. 218—220°, $[\alpha]_D$ −58° in dioxan.

This material (4·4 g.) was treated with methanesulphonyl chloride as described above. The residue left after evaporation of the ethereal solution was a solid, m. p. 125—130° (decomp.). This material was boiled under reflux for 4 hr. with a solution made by dissolving potassium (1·5 g.) in *tert.*-butanol (100 ml.). The solution was poured into water, and the product isolated with ether. Crystallisation from acetonitrile gave the *product* (V; R = H) (2·8 g., 73%), m. p. 157—169°, $[\alpha]_D$ −66·5° (Found: C, 78·3; H, 10·1. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%), $\nu_{max.}$ 1642 and 886 (1 : 1-disubstituted ethylene), 980, 920, 898, and 864 cm.$^{-1}$ (22a-spirostan) in CS_2. The presence of hydroxyl was shown by the spectrum of a Nujol mull, which had maxima at 3500 and 3280 cm.$^{-1}$.

The acetate (V; R = Ac) melted at 218—223° and had $[\alpha]_D$ −78·2°, $\nu_{max.}$ 1732 and 1238 (acetate), 1638 and 884 (1 : 1-disubstituted ethylene), 978, 918, 896, and 862 cm.$^{-1}$ (22a-spirostan) in CS_2.

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Studies of N*-Halogeno-compounds. Part VI.* The Kinetics of Chlorination of Tertiary Amines.*

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From kinetic and spectroscopic evidence the main chlorinating agent in the interaction of hypochlorous acid and trimethylamine in aqueous solution is the trimethylchlorammonium ion Me_3NCl^+ (Bohme and Krause, *Ber.*, 1951, **84**, 170). The products (cf. Crane, Forrest, Stephenson, and Waters, *J.*, 1946, 827) are dimethylchloramine and formaldehyde. Similar kinetics are observed in the chlorination of triethylamine. With tertiary amines present in excess it is found that chlorine in a solution of hydrochloric acid, present to prevent hydrolysis of the chlorine, is much less effective as a chlorinating agent than hypochlorous acid at the same pH, owing to the displacement of the equilibrium $R_3NCl^+ + Cl^- \rightleftharpoons Cl_2 + R_3N$.

A comprehensive study was made by Waters and his co-workers (*loc. cit.*) of the products of the reaction of molecular chlorine, aqueous bleaching powder, and *N*-chloroimides on various tertiary amines. They concluded that the first and slowest step was the substitution by chlorine of a hydrogen atom attached to an α-carbon atom of the amine. The α-halogenated tertiary amine rapidly decomposed to give an aldehyde and a secondary amine. With aqueous bleaching powder solution the secondary amine reacted to give the dialkylchloramine instead of being precipitated as the hydrochloride as in organic solvents. The present work has been confined to the kinetics of interaction in aqueous solution and in particular the interaction of trimethyl- and triethyl-amine with aqueous hypochlorous acid and chlorine.

With tertiary amines and halogens in carbon tetrachloride simple addition occurs to give crystalline salts of the type $[R_3NX^+]X^-$ which have been isolated by Bohme and Krause (*Ber.*, 1951, **84**, 170) (cf. Hantzsch and Graf, *ibid.*, 1905, **38**, 2154). In view of the reactivity of the analogous dialkylchlorammonium ions, R_2NHCl^+, which account for the interaction of diethylchloramine and phenols (Brown and Soper, *J.*, 1953, 3576), it was thought possible that the trialkylchlorammonium ion might play a part in the chlorination of the tertiary amine.

Experimental

The chlorine complex with trimethylamine was prepared by the method of Bohme and Krause (*loc. cit.*) by mixing the two reactants in carbon tetrachloride solution at −15°. The crystalline product was of 95% purity calculated on the iodine titre. When dry, the complex was quite stable over an examined period of 3—4 days in a darkened desiccator.

Absorption Spectra of Aqueous Trimethylchlorammonium Chloride Solutions.—The absorption curves of monochloramines, dichloramines, and nitrogen trichloride were determined by Metcalf (*J.*, 1942, 148). All have absorption maxima within the range 245—340 mμ, whilst hypochlorous acid has an absorption maximum at 235, and the hypochlorite ion (Corbett, Metcalf, and Soper, *J.*, 1953, 1927) at 295 mμ. A neutral aqueous solution of trimethylchlorammonium chloride gave the absorption spectrum of dimethylchloramine almost immediately, but in acid solutions the appearance of the dimethylchloramine was delayed. The chlorammonium chloride gave no absorption in the 220—350 mμ range, showing the absence of free chlorine or hypochlorous acid, and little change in the absorption is observable in 0·01N-sulphuric acid during 30 min. Typical absorption curves are shown in Fig. 1.

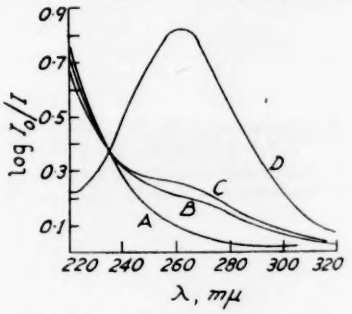
Freezing Point of Aqueous Trimethylchlorammonium Chloride.—Since in 0·01N-sulphuric acid only 3% decomposition of the complex occurs in 30 min., it is possible to examine the freezing point of solutions of the complex in acid of this concentration which itself freezes at −0·015°. A solution of 0·196M-complex of 95% purity froze at −0·780°, a lowering of 0·765° corresponding to a molarity of 0·765/1·86 = 0·41M. The high value for the freezing-point depression is in conformity with Bohme and Krause's formulation of the complex as $[R_3NCl]^+Cl^-$. The absorption curve is therefore attributed to presence of the R_3NCl^+ ion.

* Part V, *J.*, 1953, 3576.

Formation of Trimethylchlorammonium Hydroxide.—When the absorption spectrum of a solution buffered at pH 2·6 (phosphate buffer) containing equal parts of 0·01M-trimethylamine sulphate and hypochlorous acid was determined immediately after mixing, it was found to be identical with that of the trimethylchlorammonium chloride. At pH 2·6, the conversion of the mixture into dimethylchloramine is fairly slow and the curve could be obtained before 5% conversion occurred (Fig. 2). At higher pH's rapid conversion into dimethylchloramine occurred, but the curve of the trimethylchlorammonium ion appears first. There can be little doubt that on mixing trimethylamine and hypochlorous acid there is a rapid formation of the chloroammonium hydroxide, except in acid solutions such as 0·1N-sulphuric acid where the hypochlorous acid spectrum persists for over 30 min.

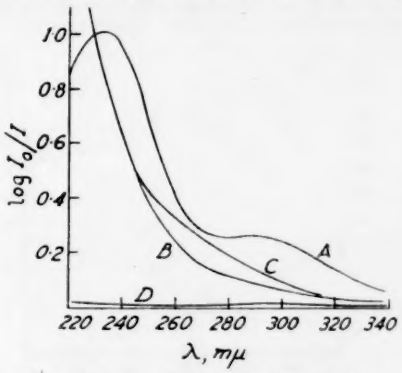
Formation of Triethylchlorammonium Hydroxide.—In contrast with the behaviour of trimethylamine, in mixtures of trimethylamine and hypochlorous acid at pH 2·8 there was little formation of the triethylchlorammonium ion within 1 hr., but in more alkaline solution, *e.g.*, pH 3·4, the characteristic absorption of this acid was replaced within 30 min. by that of the chlorammonium ion. At equal pH's the triethylchlorammonium complex in general is not formed as rapidly as the trimethylchlorammonium complex. An attempt to prepare

FIG. 1. *Absorption curves of* $Me_3NCl^+Cl^-$.



A, Immediately after solution in phosphate buffer pH 2·8.
B, After 40 min. at pH 2·8.
C, After 1 hour at pH 2·8.
D, After 30 min. at pH 6·0 (dimethylchloramine).

FIG. 2. *Absorption curves of* HOCl *and* NMe_3.



A, 0·01M-HOCl in phosphate buffer pH 2·6.
B, 0·01M-HOCl and 0·01M-$(Me_3NH)_2SO_4$ at pH 2·6 immediately after mixing.
C, As *B*, but after 20 min.
D, 0·01M-$(Me_3NH)_2SO_4$ at pH 2·6.

$[Et_3Cl]^+Cl^-$ by using Bohme and Krause's method for $[Me_3Cl^+]Cl^-$ (*loc. cit.*) did not yield a stable compound, rapid decomposition to chloramines and aldehydes occurring.

Products of the Reaction between Trimethylamine and Hypochlorous Acid.—The reaction $(CH_3)_3N + 2HOCl = (CH_3)_2NCl + H{\cdot}CHO + HCl$ requires that the loss in total oxidising power of the solution should parallel the increase in chloramine titre. The increase in the latter can be obtained by first removing the free hypochlorous acid with phenol under conditions which will leave the chloramine unaffected. That this condition is fulfilled is shown in Fig. 3, where the total oxidising power of the solution measured after treatment with potassium iodide is compared with the titre of the chloramine formed. The formaldehyde present at the end of a reaction was determined by removal of the chloramine and any residual hypochlorous acid by potassium iodide, the liberated iodine being precisely removed by sodium thiosulphate. The formaldehyde was then estimated by the bisulphite method, excess of sodium hydrogen sulphite being added and, after 45 min. to ensure complete formation of the addition compound, the uncombined bisulphite being estimated iodometrically. On use of 60 c.c. of 0·578N-hypochlorous acid (0·01783 mole of HOCl) and 0·05 mole of trimethylamine, the formaldehyde found was 0·00855 mole, corresponding to a 49·2% yield calculated on the initial hypochlorous acid. Analyses by the dimedone method gave a corresponding percentage yield of formaldehyde of 49%.

Kinetics of the Reaction.—In the examination of the effects of pH, and the concentrations of tertiary amine and hypochlorous acid at 25·00° ± 0·02° and constant ionic strength, the reaction rate was evaluated as an initial velocity, v_0, obtained either from the initial slope of the

curve obtained by plotting total titre against time or from the curve obtained by plotting the titre of dialkylchloramine produced against time (Fig. 3). These were the same within experimental error. With a constant concentration of trimethylamine of 0·01M at pH 3·40 (succinate buffer) and 0·2M-potassium nitrate present to maintain an approximately constant ionic strength, the following results were obtained for v_0 (moles l.$^{-1}$ min.$^{-1}$) in a series of runs with varying initial concentrations of hypochlorous acid :

$[HOCl]_0 \times 10^3$	0·45	1·13	1·28	2·05	2·26	3·10	4·80	6·43	8·80	9·48	14·20
$v_0 \times 10^4$	0·17	0·37	0·45	0·67	0·73	0·84	1·02	0·94	0·51	0·25	0·11

On gradual increase of [HOCl], the reaction velocity passes through a maximum at a ratio of [HOCl] to [amine] of approximately 1 : 0·5.

With a constant concentration of hypochlorous acid of 0·0024M and similar conditions of pH and ionic strength as in the above series but with varying initial concentrations of trimethylamine, added in the form of standard sulphate solution, the values of v_0 were found to be proportional to the excess concentration of amine over that of the hypochlorous acid :

$[Me_3N]_0 \times 10^3$	3·00	5·00	6·50	8·10	10·00
$([Me_3N]_0 - [HOCl]_0) \times 10^3$	0·60	2·60	4·10	5·60	7·60
$v_0 \times 10^4$	0·06	0·25	0·41	0·52	0·73

These experiments, together with those demonstrating the rapid formation of the trimethylchlorammonium ion from trimethylamine and hypochlorous acid, indicate that the reaction

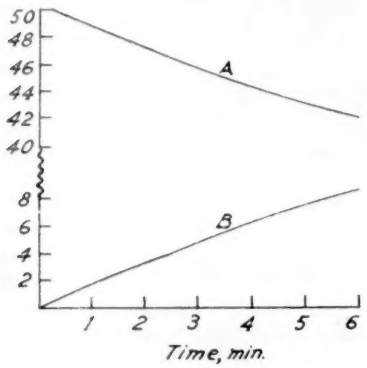


FIG. 3. *Production of* Me_2NCl: Me_3N = 0·01M; HOCl = 0·00503M; pH 3·58.
A, Fall in oxidising titre of solution.
B, Production of Me_2NCl.

rate is proportional to the product of concentrations of chlorammonium ion and the uncombined amine :

$$Me_3N + HOCl \xrightarrow{\text{Fast}} Me_3NCl^+OH^-$$

$$Me_3NCl^+ + Me_3N \xrightarrow{\text{Slow}} \text{Products} \xrightarrow{H_2O} Me_3NH^+ + Me_2NH + H{\cdot}CHO$$

$$Me_3NCl^+ + Me_2NH \xrightarrow{\text{Fast}} Me_3NH^+ + Me_2NCl$$

Kinetic equation. Over the acid range pH 3—4 where rates are convenient to measure, the excess of amine is present almost entirely in the form of its cation whilst [free amine] = $[OH^-][\text{excess of amine}]/K_b$, K_b being the classical basic ionisation constant of trimethylamine. If the initial concentration of excess of amine = $([\text{total amine}]_0 - [HOCl]_0) = [Me_3NH^+] = a$ and of chlorammonium ion $[Me_3NCl^+] = [HOCl]_0 = b$, then at time t when $[Me_2NCl] = x$, $[Me_3NH^+] = a + x$ and $[Me_3NCl^+] = b - 2x$. If a constant $k_{2(\text{obs.})}$ is defined by $v = k_{2(\text{obs.})}[\text{excess of amine}][Me_3NCl^+]$, $k_{2(\text{obs.})} = [2{\cdot}303/t(2a + b)] \log b(a + x)/a(b - 2x)$ for any one reaction at constant pH. If the kinetics involve free amine rather than amine cation, $v = k_2[Me_3N][Me_3NCl^+]$ and $k_{2(\text{obs.})} = k_2[Me_3N]/[Me_3NH^+]$, whence $k_{2(\text{obs.})}[H^+] = k_2K_w/K_b$. In this event, the product of $k_{2(\text{obs.})}$ and the hydrogen-ion concentration should be constant.

At pH 3·69 and $[Me_3N]_0$ = 0·0100, $[HOCl]_0$ = 0·00490, the following results illustrate the satisfactory nature of the rate equation for $k_{2(\text{obs.})}$, the titres marked * representing total oxidising power of the solution, and the other titres being that of dimethylchloramine formed :

Time, min.	0	0·75	2·0	3·0	3·67	4·25	4·83	5·58
Titre (c.c. of 0·02N-$Na_2S_2O_3$) of 10 c.c.	49·00*	1·60	4·20	6·12	7·35	8·33	9·20	39·80*
$k_{2\,(\text{obs.})}$	—	8·70	8·75	8·85	8·8	8·8	8·75	—

Experiments on the variation of $k_{2(obs.)}$ with pH showed that in the range pH 3—4 the rate is proportional, as in the interaction of hypochlorous acid and dialkylamines, to the hydroxyl-ion concentration of the buffered solution. This indicates that the reaction rate involves the free amine base as opposed to the amine cation. With initial concentrations of trimethylamine of $1{\cdot}00 \times 10^{-3}$M and hypochlorous acid of $0{\cdot}50 \times 10^{-3}$M, the initial rate, v_0, and the rate constants $k_{2(obs.)}$ for the reactions in the acid range varied as follows :

pH	3·04	3·37	3·58	3·69	3·97	5·0—12·0
$v_0 \times 10^4$	0·45	1·05	1·5	2·1	4·0	Very fast
$k_{2(obs.)}$	1·98	4·15	6·46	8·81	16·6	—
$k_{2(obs.)} \times [H^+]$	17·2	17·7	17·0	17·9	$17{\cdot}8 \times 10^{-4}$	—

The rate in more alkaline solutions decreases and becomes measurable above pH 12. This is probably due to the displacement of the equilibrium $Me_3NCl^+ + OH^- \longrightarrow Me_3N + HOCl$ and the conversion of HOCl into OCl^-, resulting in removal of the chlorammonium ion from the system. The values of v_0 with concentrations as above and $[OH^-]$ equal to 0·025, 0·05, 0·10, and 0·20 are respectively 9·5, 3·0, 0·89, and $0{\cdot}46 \times 10^{-4}$ for solutions in which sodium hydroxide is present. These systems in strongly alkaline solution are too unstable for very accurate measurement.

With a constant initial concentration of 0·0100M-trimethylamine added as sulphate and

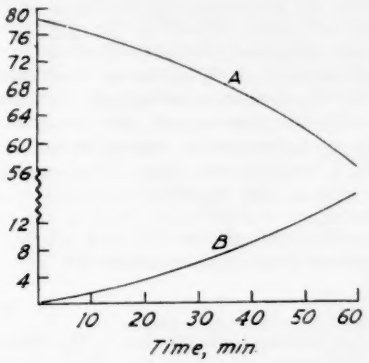


FIG. 4. $Et_3N = 0{\cdot}01$M; HOCl = 0·00794M; pH 3·40, *showing autocatalysis.*
A, Total titre.
B, :NCl titre.

varying initial concentrations of hypochlorous acid, mean values for $k_{2(obs.)}$ at pH 3·40 for several experiments are given below :

$[HOCl] \times 10^3$	0·45	1·13	2·26	3·10	4·81	6·43	8·80	9·48
$k_{2(obs.)}$	4·10	4·16	4·36	4·30	4·44	4·50	4·76	4·84

Within each experiment the individual values of $k_{2(obs.)}$ were reasonably constant. However, $k_{2(obs.)}$ tends to increase gradually when the hypochlorous acid concentration approaches that of the amine and, owing to formation of the chlorammonium ion, the concentration of free amine becomes low. Under these conditions the autodecomposition of the chlorammonium cation itself would result in higher values for $k_{2(obs.)}$ at low concentrations of free amine.

Results with Triethylamine.—Although the rate of reaction of hypochlorous acid with triethylamine shows the same general dependence on the excess of amine over that of the hypochlorous acid and also on the alkalinity of the solution, the kinetic results are complicated by the fact that the triethylchlorammonium ion is not formed rapidly and quantitatively in the pH range studied, as shown from the ultra-violet absorption curves. The chlorammonium salt is formed more rapidly in the less acidic solution. The consecutive reactions $HOCl + Et_3N \longrightarrow Et_3NCl^+ + Cl^-$; $Et_3NCl^+ + Et_3N \longrightarrow$ Products, thus overlap, and the rate of chlorination and of production of Et_2NCl both show evidence of autocatalysis (Fig. 4). The relation of the initial rate of production of diethylchloramine, v_0, to increasing initial concentration of hypochlorous acid and a fixed concentration of triethylamine $= 10^{-2}$M at pH 3·40 is given below :

$[HOCl] \times 10^3$	1·07	2·69	4·96	7·94	8·24	10·8	15·3	20·6	30·0
$v_0 \times 10^4$	0·07	0·12	0·14	0·15	0·14	0·13	0·11	0·07	0·01

This rate is approximately 0·65 times that of the rate of total loss of oxidising power by the solution but diminishes as the ratio of hypochlorous acid to triethylamine increases. With trimethylamine the rate of formation of dialkylchloramine equals the total loss of oxidising power of the solution. Whereas with trimethylamine a maximum rate was observed when the initial concentration of hypochlorous acid is half that of the amine, yet the maximum initial rate with triethylamine instead of occurring at this point, *viz.*, 5×10^{-3}M, appears at a higher concentration of hypochlorous acid. This is due to the greater relative time required to form the chlorammonium ion, and to its formation being assisted by higher concentrations of hypochlorous acid.

The Relative Chlorinating Efficiencies of the Chlorammonium Ion and Chlorine.—When to a series of mixtures of 10^{-2}M-trimethylamine and $0{\cdot}5 \times 10^{-2}$N-hypochlorous acid at pH 2·45 increasing amounts of potassium chloride were added, the yellow colour and odour of chlorine developed, and the reaction rate diminished as set out below, potassium nitrate being present to maintain constant ionic strength :

KCl, N	0·00	0·09	0·18	0·45	0·90	1·35	1·80
KNO_3, N	1·80	1·71	1·62	1·35	0·90	0·45	0·00
$v_0 \times 10^4$	2·35	2·25	2·20	1·95	1·40	1·10	0·90

Spectrophotometric examination of the mixture containing 1·80M-potassium chloride showed first the formation of the chlorammonium ion on mixing of the amine and hypochlorous acid, and then the production of chlorine on addition of potassium chloride. Evidently a reversible equilibrium exists, $R_3NCl^+ + Cl^- \rightleftharpoons R_3N + Cl_2$. Comparison of the spectra with those of standard solutions of chlorine showed that the addition of 1·80N-potassium chloride resulted in approximately 60% of the active chlorine being present as chlorine.

Since the remainder of the active chlorine, *i.e.*, 40%, is in the form of chlorammonium ion, the reduction in the reaction rate from 2·35 to 0·90 is paralleled by the reduction in the amount of the rate-determining chlorammonium ion. One explanation of this result is that the Me_3NCl^+ ion is a much more effective chlorinating agent than molecular chlorine. The displacement of the equilibrium $R_3NCl^+ + Cl^- \rightleftharpoons R_3N + Cl_2$ in solutions of high chloride concentration explains the anomalous and at first sight puzzling result that with excess of amine present hypochlorous acid is more efficient in reaction with tertiary amines than solutions of chlorine to which chloride is added to prevent chlorine hydrolysis.

Discussion

The kinetics indicate clearly that the interaction of hypochlorous acid or chlorine and trimethylamine involves the chlorammonium cation. In mixtures of amine and hypochlorous acid the rate is also dependent on the concentration of free amine base. Whether this base is always a necessary reactant is uncertain, for solutions of the chlorammonium chloride in the absence of added amine also decompose to form the dimethylchloramine at pH 7. Moreover, there is some evidence that the rate, in mixtures of chlorammonium cations and free amine, is not strictly proportional to the free amine concentration except where this concentration is high. At lower concentrations of free amine, a direct decomposition of the chlorammonium ion also appears to be of importance.

There appear to be two reaction possibilities which conform to the observed kinetics. In the first the chlorammonium ions act as a highly efficient electrophilic chlorinating agent, chlorinating alkyl groups in the tertiary amine. If the chlorination is in the α-position, hydrolysis follows with production of the aldehyde and secondary amine, which in the presence of the efficient chlorinating agent is converted very rapidly into the dialkylchloramine. This would require equality of rates of α-chlorination and production of dialkylchloramine if the rate-determining step is α-chlorination. If chlorination at β-carbon atoms also occurs as well as α-chlorination, the rate of carbon chlorination will exceed that of dialkylchloramine formation. It is observed with trimethylamine, where chlorination must be confined to the α-carbon atom, that the two rates are equal whereas in triethylamine the rate of *C*-chlorination as given by the loss of active chlorine in the solution is about 1·5—1·6 times that of the formation of diethylchloramine. The production of other chlorinated products isolated by Waters and his co-workers (*loc. cit.*) would be in harmony with an attack by a halogenating agent on one of the alkyl groups of the tertiary amine.

The alternative explanation is based on Bohme and Krause's suggestion (*loc. cit.*) that the trimethylchlorammonium halide decomposes as follows :

$$[\overset{+}{N}Me_2X{\cdot}CH_3]\bar{X} \xrightarrow{-XH} \overset{+}{N}Me_2X{\cdot}\bar{C}H_2 \longrightarrow NMe_2{\cdot}CH_2X \longrightarrow \overset{+}{N}Me_2H_2\ \bar{X} + H{\cdot}CHO$$

The dependence of the rate on the free amine concentration may on this view be due to its action as a proton acceptor removing a proton from an α-carbon atom :

$$Me_2\overset{+}{N}\begin{matrix}CH_3\\Cl\end{matrix} + NR_3 \xrightarrow{\text{Slow}} Me_2\overset{+}{N}\begin{matrix}CH_2^-\\Cl\end{matrix} + HNR_3^+ \longrightarrow \text{Products}$$

This mechanism of proton removal from the chlorammonium ion would also explain the surprising result that when the chlorammonium ion is partially converted into chlorine by displacement of the equilibrium $R_3NCl^+ + Cl^- \longrightarrow Cl_2 + R_3N$, the reaction is made slower in proportion to the conversion of the chlorammonium ion into chlorine. On the first hypothesis, on the other hand, in order to explain this result one must assume that, in comparison with the chlorammonium ion, chlorine is relatively inactive as a chlorinating agent. This is unlikely in view of the relative ease of the ionisation of chlorine and of the chlorammonium ion into positive chlorine. If K_1 is the equilibrium constant of $Cl_2 \rightleftharpoons Cl^+ + Cl^-$ and K_2 that of $Me_3NCl^+ \rightleftharpoons Me_3N + Cl^+$, the ratio K_1/K_2 is given by the equilibrium constant of $Me_3N + Cl_2 \rightleftharpoons Cl^- + Me_3NCl^+$. The spectroscopic determination of the free chlorine in solutions of the chlorammonium ion in the presence of 1·8N-potassium chloride gives a value for this equilibrium constant of approximately $1{\cdot}5 \times 10^2$. Although this figure refers to the solvated ions, it would be expected that a chlorine would form positive chlorine at the seat of the reaction, if not more easily than, at least as easily as, the trimethylchlorammonium ion. This would indicate that the hypothesis of direct chlorination as the rate-determining step in dealkylation is unlikely. Further work on the relative efficiencies of chlorine and the chlorammonium ion is proceeding.

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The Pyrone Series. Part I. 2 : 6-*Diaryl*-4-*pyrones.*

By GABRA SOLIMAN and IBRAHIM EL-SAYED EL-KHOLY.

[Reprint Order No. 4810.]

Previous syntheses of 2 : 6-diphenylpyrone have a limited preparative value. This and five new 2 : 6-diaryl-4-pyrones have now been obtained in good yields by condensation of ethyl phenylpropiolate with the acetophenones at 0°; two of the new pyrones are accompanied by the isomeric acetylenic diketones (IV). The diarylpyrones give picrates and *N*-hydroxypyridones, and are hydrolysed with potassium hydroxide to ketones and acids, the isolation of which indicates the mode of cleavage.

2 : 6-DIPHENYL-4-PYRONE, which appears to be the only known 2 : 6-diaryl-4-pyrone, was first obtained in traces by Feist (*Ber.*, 1890, **23**, 3726) by heating dehydrobenzoylacetic acid with mineral acids, but unlike the 2 : 6-dimethyl analogue (Feist, *Annalen*, 1890, **257**, 282), it could not be obtained by decarboxylation of the 3 : 5-dicarboxylic acid. In an attempt to find a general synthesis of 2 : 6-diaryl-4-pyrones, Vorländer and Meyer's poor yield of 2 : 6-diphenylpyrone (*Ber.*, 1912, **45**, 3355) could not be improved; also di-*p*-anisylideneacetone tetrabromide failed to give 2 : 6-di-*p*-methoxyphenyl-4-pyrone (cf. Vorländer and Mumme, *Ber.*, 1903, **36**, 1475); equally, Ruhemann's synthesis of 2 : 6-diphenylpyrone (*J.*, 1908, **93**, 431), which appeared to be a suitable alternative, did not lead

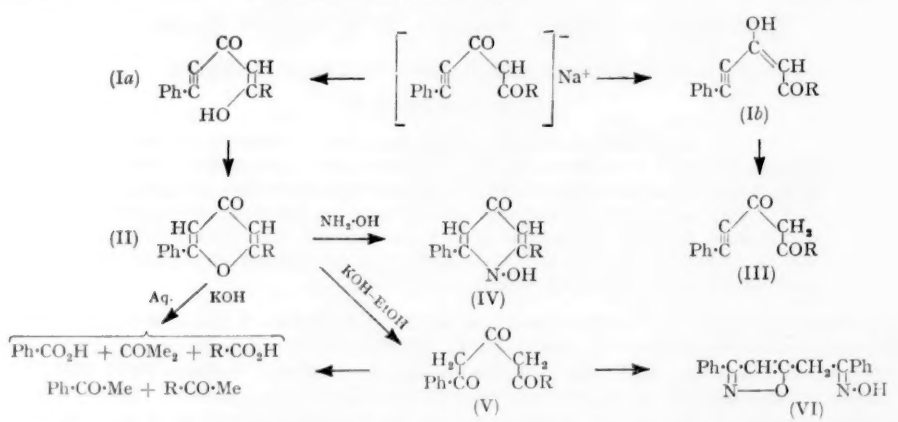
satisfactorily to this pyrone. Meanwhile, we failed to isolate the unidentified product, $C_{25}H_{20}O_3$, whose formation was attributed to the condensation of two mols. of acetophenone with one of ethyl phenylpropiolate.

In the present investigation, it has been possible to prepare 2 : 6-diphenylpyrone in about 50% yield by condensing acetophenone with ethyl phenylpropiolate at 0° in presence of sodium ethoxide in ether. Analogously, 2-phenyl-6-*p*-tolyl-4-pyrone (which could not be prepared by Ruhemann, *J.*, 1910, **97**, 457), 2-*p*-methoxyphenyl-, 2-*p*-chlorophenyl-, 2-*p*-bromophenyl-, and 2-*p*-iodophenyl-6-phenyl-4-pyrones were prepared in satisfactory yields by using substituted acetophenones. 6-Phenylindeno(3′ : 2′-2 : 3)pyrone (Ruhemann, *J.*, 1912, **101**, 1729) was also prepared in 80% yield, and gave a picrate just as the 2 : 6-diarylpyrones did. On the other hand, ethyl phenylpropiolate failed to condense with ethyl methyl ketone or propiophenone.

In each of the above cases, when the reaction mixture was mixed with water, most of the pyrone separated from the alkaline solution on standing or on saturation with carbon dioxide. Evidently, liberation of the pyrone in this manner is due to hydrolysis of a sodio-derivative of the intermediate acetylenic diketone and subsequent rearrangement of the free enol (I*a*) to (II). Otherwise, hydrolysis might lead to (I*b*) which would rearrange to the keto-form (III). The formation of such acetylenic diketones is explicable in the light of the modern interpretation of the Claisen condensation (Arndt and Eistert, *Ber.*, 1936, **69**, 2381; Hauser, *J. Amer. Chem. Soc.*, 1937, **59**, 1823; 1938, **60**, 1957).

The isomeric acetylenic diketone could not be isolated in the case of diphenylpyrone, yet variable amounts of 5-phenyl-1-*p*-tolylpent-4-yne-1 : 3-dione (III; R = *p*-C_6H_4Me) and the methoxyphenyl and bromophenyl analogues accompanied the corresponding pyrones. Those ketones are characterised by their oximes and by their solubility in cold alcoholic alkali, although they do not give a positive test with ferric chloride. Further, they were converted into the pyrones under the conditions stated on p. 1759.

Whereas the conversion of 1 : 4-pyrones into pyridones by the action of aqueous ammonia or ammonium acetate is a general reaction, 2 : 6-diaryl-4-pyrones were resistant to these reagents. 2 : 6-Diphenyl-4-pyridone, however, was prepared indirectly by the action of aqueous ammonia on dehydrobenzoylacetic acid or 2 : 6-diphenyl-4-pyrone-carboxylic acid (Petrenko-Kritschenko and Schöttle, *Ber.*, 1909, **42**, 2020; 1911, **44**, 2826, 3648). Similarly, 2 : 6-diarylpyrones did not react with aniline acetate, whereas the other 1 : 4-pyrones readily give *N*-phenylpyridones (Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 599; Borsche and Peter, *Annalen*, 1927, **453**, 148).



The inertness of the carbonyl group of 1 : 4-pyrones towards carbonyl reagents is in harmony with their resonance formulæ. 2 : 6-Diphenylpyrone oxime, however, was prepared by the action of hydroxylamine on 2 : 6-diphenyl-4-thiopyrone which behaves as a true thioketone (Arndt, Nachtwey, and Scholz, *Ber.*, 1924, **57**, 1903). This yellowish

oxime, m. p. 197°, is different from a white isomer, m. p. 181°, which we have prepared by the action of hydroxylamine on 2 : 6-diphenylpyrone. Evidently, formation of the latter isomer must have involved the oxidic oxygen and would be 1-hydroxy-2 : 6-diphenylpyridone (IV; R = Ph). Other 2 : 6-diaryl-*N*-hydroxypyridones were also prepared and they appear to be analogous to some known *N*-substituted pyridones (Peratoner and Tamburello, *Gazzetta*, 1911, **41**, II, 666; Bedekar, Kaushall, and Deshapande, *J. Indian Chem. Soc.*, 1935, **12**, 465).

Unlike 1 : 4-pyrone, 2 : 6-dimethylpyrone, and 2-methyl-6-phenylpyrone which undergo ring fission to the corresponding triketones by the action of barium hydroxide, 2 : 6-diphenylpyrone was recovered unchanged. Nevertheless, Balenović and Munk (*Archiv Kemiju*, 1946, **18**, 41) prepared *s*-dibenzoylacetone by the action of potassium hydroxide in aqueous methanol: we have prepared the same trione under milder conditions. *s*-Dibenzoylacetone (V; R = Ph) gave with hydroxylamine a crystalline substance, m. p. 145°, the analysis of which is in agreement with the formula (VI) comprising an oxime group and an *iso*oxazole ring.

s-Dibenzoylacetone was readily hydrolysed with boiling aqueous potassium hydroxide to acetone, acetophenone, and benzoic acid. Apparently, acetone and benzoic acid arise from a symmetrical cleavage of the triketone, whereas cleavage between $C_{(2)}$ and $C_{(3)}$ or between $C_{(3)}$ and $C_{(4)}$ leads to acetophenone directly or through decarboxylation of benzoylacetic acid. The same hydrolysis products were also obtained from 2 : 6-diphenylpyrone, and this is evidence in favour of the formation of triketones before the degradation of the pyrones. The other 2 : 6-diarylpyrones were more resistant to the action of the alkali, but their hydrolysis products indicate that they undergo the same mode of cleavage.

Experimental

Light petroleum used had b. p. 60—80°.

2 : 6-*Diphenylpyrone*.—When ethyl phenylpropiolate and acetophenone were condensed as described by Ruhemann, the total yield of the pyrone as hydrochloride and as picrate was 12%.

Acetophenone (3·5 g., 1 mol.) and ethyl phenylpropiolate (5 g., 1 mol.) were successively added to an ice-cold suspension of sodium ethoxide (1·95 g., 1 mol.), and the the mixture was kept in the ice-chest for 2 days, then mixed with water. The ethereal solution was washed and evaporated. The reddish oil (2·5 g.) recovered gave traces of the pyrone as picrate. The alkaline solution and washings gradually became turbid and in 6—8 hr. the pyrone separated almost completely; this could be enhanced by saturation with carbon dioxide. The pyrone (50%) crystallised from benzene–light petroleum in needles, m. p. 140° (Found: C, 81·9; H, 5·0. Calc. for $C_{17}H_{12}O_2$: C, 82·2; H, 4·9%). The alkaline mother-liquor yielded 1 g. of phenylpropiolic acid.

2 : 6-*Diphenylpyrone picrate* was prepared in alcohol and crystallised from benzene in yellow needles, m. p. 183° (Found: C, 57·8; H, 3·2; N, 9·1. $C_{23}H_{15}O_9N_3$ requires C, 57·8; H, 3·2; N, 8·8%); it was hydrolysed to the pyrone when its alcoholic solution was warmed with dilute aqueous ammonia.

1-*Hydroxy*-2 : 6-*diphenylpyridone*.—This was prepared when an alcoholic solution of the pyrone (0·8 g.) was heated for 6 hr. with hydroxylamine hydrochloride (0·8 g.) and sodium acetate (0·8 g.) in water (3 ml.). The *pyridone* (50% yield), which crystallised on cooling, was washed with ether. It recrystallised from benzene–methanol in needles, m. p. 181°, depressed on admixture with 2 : 6-diphenylpyrone oxime (Arndt, Nachtwey, and Scholz, *loc. cit.*) (Found: N, 5·2. $C_{17}H_{13}O_2N$ requires N, 5·3%).

2 : 6-Diphenylpyrone was recovered unchanged after being heated with ammonium acetate in acetic acid for 10 hr. at 100°, or with aniline acetate in acetic acid for 8 hr. at 100°. When a mixture of the pyrone (0·5 g.), barium octahydrate (0·5 g.), and water (100 ml.) was boiled for 10 min., and then filtered, and the same process was repeated 5 times, 0·35 g. remained unchanged. The combined filtrates gave traces of acetophenone on distillation with steam.

s-*Dibenzoylacetone*.—This was obtained when a solution of the pyrone (1 g.) in absolute alcohol (15 ml.) and 10% alcoholic potassium hydroxide (10 ml.) was kept at room temperature for 2 days. The alcohol was then distilled under reduced pressure, the residue mixed with water and extracted with ether, and the alkaline solution acidified. The triketone (0·6 g.)

crystallised from light petroleum in yellow plates, m. p. 111° (cf. Balenović and Munk, *loc. cit.*) (Found : C, 76·5; H, 5·3. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%). It was also prepared by the action of alcoholic sodium ethoxide.

The iso*Oxazole Oxime* (VI).—5-(2-*Hydroxyimino*-2-*phenylethyl*)-3-*phenyl*iso*oxazole* was obtained when an alcoholic solution of *s*-dibenzoylacetone (0·2 g.) was heated for 3 hr. with hydroxylamine hydrochloride (0·2 g.) and sodium acetate (0·2 g.). It crystallised from light petroleum in prisms, m. p. 145° (Found : C, 73·3; H, 4·9; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·1; N, 10·1%).

s-Dibenzoylacetone (0·3 g.) was completely hydrolysed when boiled with 5% aqueous potassium hydroxide (10 ml.) for 1 hr. Its degradation products, acetone, acetophenone, and benzoic acid, were identified as described below.

Action of 20% *Aqueous Potassium Hydroxide* on 2 : 6-*Diphenyl*-4-*pyrone*.—The pyrone (1 g.) was refluxed with 20 ml. of the alkali in an all-glass apparatus for 4 hr. The mixture was then steam-distilled, the first 100 ml. and the next 400 ml. of the ketonic distillate being collected separately. Subsequently, the alkaline mixture was freed from the unchanged pyrone and resin (0·1 g.) by extraction with ether, acidified with 10% sulphuric acid, and steam-distilled until 1 l. of the acidic distillate had collected. The first ketonic distillate was freed from acetophenone by extraction with ether and treated with the vanillin reagent (Snell : "Colorimetric Methods of Analysis," Van Nostrand, New York, 1937, Vol. II, p. 96); it developed the reddish-brown colour specific for acetone.

In another identical experiment, the total ketonic distillate gave 1·4 g. of a mixed 2 : 4-dinitrophenylhydrazone, m. p. 180—190°, which were extracted with hot alcohol. The solution gave on concentration acetone 2 : 4-dinitrophenylhydrazone which crystallised from dilute alcohol in yellow needles, m. p. and mixed m. p. 124°. The insoluble residue crystallised from acetic acid in red needles, m. p. 247°, identical with acetophenone 2 : 4-dinitrophenylhydrazone.

The acidic distillate from either of the two experiments gave a negative test for acetic acid and about 0·5 g. of benzoic acid.

2-p-*Methoxyphenyl*-6-*phenyl*-4-*pyrone*.—*p*-Methoxyacetophenone (4·3 g.) and ethyl phenylpropiolate (5 g.) were condensed as for diphenylpyrone. The mixture was mixed with water, and the suspended precipitate was shaken with ether and water. The oily residue (4·3 g.) recovered from the ethereal solution gave a yellow solid (1·7 g.), m. p. 135°, on treatment with cold methanol. The alkaline solution and washings deposited a yellowish precipitate (1·8 g.), m. p. 140—145° after being washed with cold ether. The average yield of solids including the pyrone recovered as picrate was 50%. The solid products gave on fractional crystallisation from methanol, ethanol, or benzene the diketone (III; R = *p*-C_6H_4·OMe), m. p. 138°, which crystallised first, and the pyrone, m. p. 150—152°, which was recovered from the mother-liquors. The *pyrone* recrystallised from benzene in sulphur-yellow rhombs, m. p. 160—161°, which recrystallised from 5% alcoholic potassium hydroxide almost unchanged (Found : C, 77·6; H, 5·2; OMe, 11·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1; OMe, 11·2%). It dissolved in hot hydrochloric acid and, on cooling, the *pyrone hydrochloride* separated in golden-yellow needles, m. p. 185° (Found : Cl, 10·5. $C_{18}H_{15}O_3Cl$ requires Cl, 11·3%). The hydrochloride was readily hydrolysed to the pyrone. The *pyrone picrate* was prepared in alcohol or benzene and crystallised from benzene in orange needles, m. p. 202° (Found : N, 8·3. $C_{24}H_{17}O_{10}N_3$ requires N, 8·3%). It gave the free pyrone with aqueous ammonia.

1-*Hydroxy*-2-p-*methoxyphenyl*-6-*phenylpyridone* was prepared as described above and crystallised from benzene in needles, m. p. 185° (Found : C, 73·5; H, 5·4; N, 4·6. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2; N, 4·8%).

By the action of 20% aqueous potassium hydroxide as above, about half of the 2-*p*-methoxyphenyl-6-phenyl-4-pyrone used was hydrolysed. The ketonic distillate gave a positive test for acetone and a mixed 2 : 4-dinitrophenylhydrazone, m. p. 190—200°, from which *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 207—208°, was isolated after extraction with hot alcohol and fractional crystallisation from acetic acid. The acidic distillate gave benzoic acid, but the less volatile *p*-anisic acid, m. p. 184°, was isolated from the acidic mixture by extraction with ether.

1-p-*Methoxyphenyl*-5-*phenylpent*-4-*yne*-1 : 3-*dione* (III).—The *diketone* crystallised from alcohol in yellow cubes or from benzene in yellow needles, m. p. 140°, which gave a negative test with ferric chloride (Found : C, 77·5; H, 5·2. $C_{18}H_{14}O_3$ requires C, 77·5; H, 5·1%). It was recovered unchanged after treatment with ammonium acetate or aniline acetate, and did not give a picrate. The oxime was isolated when a solution of the diketone (0·5 g.) in alcohol was heated for 4 hr. with hydroxylamine hydrochloride (0·5 g.) and sodium acetate (0·5 g.). It

crystallised from benzene–light petroleum in yellowish needles, m. p. 187° (Found : C, 73·7; H, 5·3; N, 4·8. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·2; N, 4·8%).

The diketone readily dissolved in 5% alcoholic potassium hydroxide, and after the reddish-brown solution had been diluted with water the resinous precipitate was extracted with ether. The residue recovered from the ethereal solution gave with picric acid a reddish-orange precipitate from which the pyrone picrate, m. p. 202°, was isolated by crystallisation.

2-Phenyl-6-p-tolyl-4-pyrone.—Methyl *p*-tolyl ketone (3·85 g.) and ethyl phenylpropiolate (5 g.) were condensed at 0°, and the product worked up as before. The oil (3 g.) recovered from the ethereal solution gave, on cooling, a yellowish solid (0·7 g.), m. p. 129°, after being washed with ether. The alkaline solution deposited 3·4 g. of a brownish-yellow solid, m. p. 127—137°. The average yield including pyrone recovered as picrate was 57%. These solids gave on fractional crystallisation from methanol the diketone (III; R = *p*-C_6H_4Me), m. p. 133°, which crystallised first, and the pyrone, m. p. 145—147°, which was recovered from the mother-liquors.

The *pyrone* crystallised from benzene–light petroleum in yellowish needles, m. p. 150°, which recrystallised almost unchanged from 5% alcoholic potassium hydroxide (Found : C, 82·6; H, 5·4. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). Its *picrate* crystallised from alcohol in yellow needles, m. p. 195° (Found : N, 8·7. $C_{24}H_{17}O_9N_3$ requires N, 8·6%).

1-Hydroxy-2-phenyl-6-p-tolylpyridone was prepared by the action of hydroxylamine on the pyrone in alcohol, and crystallised from benzene in needles, m. p. 184° (Found : N, 4·8. $C_{18}H_{15}O_2N$ requires N, 5·1%).

This pyrone was partly hydrolysed with 20% potassium hydroxide. The ketonic distillate gave a positive test for acetone, and a 2 : 4-dinitrophenylhydrazone which crystallised from acetic acid in red needles, m. p. 228—233°, elevated on admixture with the 2 : 4-dinitrophenylhydrazones of acetophenone or methyl *p*-tolyl ketone. In addition to benzoic acid, *p*-toluic acid, m. p. 181°, was isolated from the acidic mixture.

5-Phenyl-1-p-tolylpent-1-yne-1 : 3-dione recrystallised from benzene–light petroleum in pale yellowish prismatic needles, m. p. 133°, which gave a negative test with ferric chloride (Found : C, 82·3; H, 5·3. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). Its *oxime* crystallised from benzene in needles, m. p. 190° (Found : C, 77·7; H, 5·5; N, 5·2. $C_{18}H_{15}O_2N$ requires C, 77·9; H, 5·5; N, 5·1%).

When a cold saturated solution of the diketone in alcohol or benzene was mixed with the respective solution of picric acid, the pyrone picrate gradually separated. The diketone was also converted into the pyrone when its solution in alcoholic potassium hydroxide was diluted with water.

2-p-Chlorophenyl-6-phenyl-4-pyrone.—This *pyrone* was prepared in 90% yield by condensation of *p*-chloroacetophenone (4·45 g.) with ethyl phenylpropiolate (5 g.). It crystallised from benzene or carbon tetrachloride in pale yellowish needles, m. p. 160° (Found : C, 71·2; H, 4·1; Cl, 12·9. $C_{17}H_{11}O_2Cl$ requires C, 72·2; H, 3·9; Cl, 12·6%). Better analyses for carbon could not be obtained irrespective of repeated crystallisation or dehydration. The *pyrone picrate* crystallised from alcohol in yellow needles, m. p. 177° (Found : N, 8·3. $C_{23}H_{14}O_9N_3Cl$ requires N, 8·3%). *1-Hydroxy-2-p-chlorophenyl-6-phenylpyridone*, prepared as above, crystallised from benzene in needles, m. p. 188—190° (Found : N, 4·4. $C_{17}H_{12}O_2NCl$ requires N, 4·7%).

2-p-Bromophenyl-6-phenyl-4-pyrone.—The *bromo*-compound was prepared in 80% yield from *p*-bromoacetophenone (5·7 g.) and ethyl phenylpropiolate (5 g.) and crystallised from benzene in yellowish needles, m. p. 172° (Found : C, 62·4; H, 3·5; Br, 23·9. $C_{17}H_{11}O_2Br$ requires C, 62·4; H, 3·4; Br, 24·4%). Its *picrate* crystallised from alcohol in yellow needles, m. p. 163° (Found : N, 7·7. $C_{23}H_{14}O_9N_3Br$ requires N, 7·6%). *2-p-Bromophenyl-1-hydroxy-6-phenyl-4-pyridone*, prepared as usual, crystallised from benzene in needles, m. p. 183° (Found : N, 4·2. $C_{17}H_{12}O_2NBr$ requires N, 4·1%).

During the purification of the pyrone by fractional crystallisation from alcohol, traces of *1-p-bromophenyl-5-phenylpent-4-yne-1 : 5-dione* were obtained. This recrystallised from benzene in yellow needles, m. p. 190° (Found : C, 62·5; H, 3·4; Br, 24·0. $C_{17}H_{11}O_2Br$ requires C, 62·4; H, 3·4; Br, 24·4%).

2-p-Iodophenyl-6-phenyl-4-pyrone.—This *compound* was prepared in 75% yield by condensing *p*-iodoacetophenone (Kimura, *Ber.*, 1934, **67**, 395) with the ester at 0°, and crystallised from benzene in lemon-yellow needles, m. p. 191° (Found : C, 54·7; H, 3·2; I, 33·9. $C_{17}H_{11}O_2I$ requires C, 54·5; H, 3·0; I, 33·9%).

The halogen-containing pyrones were more resistant to the action of potassium hydroxide, and the portions hydrolysed gave positive tests for acetone and mixed 2 : 4-dinitrophenyl-

hydrazones. Together with benzoic acid, *p*-chlorobenzoic, *p*-bromobenzoic, and *p*-iodobenzoic acid respectively were also isolated.

6-*Phenylindeno*(3′ : 2′-2 : 3)*pyrone*.—This was prepared in 80% yield by condensation at 0°, and gave a *picrate* which crystallised from alcohol in yellow prisms, m. p. 217° (Found : N, 8·9. $C_{24}H_{15}O_9N_3$ requires N, 8·6%).

Attempts to condense ethyl methyl ketone or propiophenone with ethyl phenylpropiolate at 0° led to oils which did not give pyrones as hydrochlorides or picrates.

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Studies on Biological Methylation. Part XIV. The Formation of Trimethylarsine and Dimethyl Selenide in Mould Cultures from Methyl Sources containing* ^{14}C.

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The mechanism of the production of trimethylarsine and dimethyl selenide in bread cultures of *S. brevicaulis*, and of dimethyl selenide in cultures of *Aspergillus niger* on liquid media or on bread, has been studied by the use of choline chloride, betaine, sodium formate, and DL-methionine as potential sources of the methyl group labelled with ^{14}C. The mercurichlorides of the trimethylarsine and dimethyl selenide were radioactive in each case. The activity was very considerable with methionine, from which the $^{14}CH_3$ is probably transferred intact to arsenic and selenium. Addition of [^{14}C]choline and [^{14}C]formate to cultures of *S. brevicaulis* containing diethyl disulphide or *S*-ethylcysteine gave inactive ethanethiol and radioactive ethyl methyl sulphide.

WORK carried out in Leeds since 1931 has established that in bread cultures of the mould *Scopulariopsis brevicaulis* arsenious oxide or sodium arsenate, sodium selenate or selenite, and potassium tellurate or tellurite are converted into trimethylarsine, dimethyl selenide, and dimethyl telluride respectively. These volatile products were characterised as the mercurichlorides. Numerous other derivatives were also employed for this purpose [Challenger, Higginbottom, and Ellis, *J.*, 1933, 95; Challenger and Higginbottom, *Biochem. J.*, 1935, **29**, 1757; Challenger and North, *J.*, 1934, **68**; Bird and Challenger, *J.*, 1939, 163].

Methylation is also observed with the alkylarsonic and dialkylarsinic acids, $R{\cdot}AsO(OH)_2$ and $RR'AsO{\cdot}OH$, giving $AsRMe_2$ and $AsRR'Me$, and with the alkaneseleninic acids $R{\cdot}SeO_2H$ giving SeRMe, where R and/or R′ = Me, Et, or Pr^n [Challenger and Ellis, *J.* 1935, 396; Challenger and Rawlings, *J.*, 1936, 264; Bird and Challenger, *J.*, 1942, 574]. Other moulds (including *Aspergillus niger* and *Penicillium notatum*) which can effect one or more of these methylations are cited by Bird, Challenger, Charlton, and Smith (*Biochem. J.*, 1948, **43**, 78).

The methylating action of *S. brevicaulis* is also exerted on aliphatic disulphides $RS{\cdot}SR$ (R = Me to n-C_5H_{11}) and on *S*-alkylcysteines $RS{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$ (R = Me to Pr^n) giving RSH and SRMe in each case (Challenger and Rawlings, *J.*, 1937, 868; Challenger and Charlton, *J.*, 1947, 424). Methionine $MeS{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$ also yields methanethiol and dimethyl sulphide. The importance of the last result will be considered below.

These results, and experiments designed to test the hypotheses which were put forward to explain them, have been discussed by one of us in various reviews (*Chem. and Ind.*, 1942, 399, 413, 456; *Chem. Reviews*, 1945, **36**, 315; *Ann. Reports*, 1946, **43**, 262; *Adv. Enzymology*, 1951, **12**, 429). It seemed possible that formaldehyde, glyoxylic acid, or some closely related compound (Robinson's " formaldehyde equivalent," *J.*, 1917, **111**, 879; *J. Roy. Soc. Arts*, 1948, **96**, 796; IX Int. Congr. Pure and Appl. Chem., Madrid, 1934), arising

* Part XIII, Challenger and Liu, *Rec. Trav. chim.*, 1950, **69**, 334.

from glycine or possibly from purines, might by reaction with arsenious acid yield $HO{\cdot}CH_2{\cdot}AsO_3H_2$. This on reduction might give $Me{\cdot}AsO_3H_2$. Repetition of the process would finally yield trimethylarsine. Similar arguments could be employed to explain the formation of the methylated sulphur, selenium, and tellurium compounds. Conclusive evidence in favour of this hypothesis was difficult to obtain and attention was gradually focused on a mechanism involving the loss of a methyl group from some labile methyl compound present in the mould cell, followed by its attachment as such to arsenic and other elements. This was discussed by one of us and Higginbottom in 1935, and again in 1942.

The suggestion of a methyl transfer in animal metabolism was first advanced by Hofmeister (*Arch. exp. Path. Pharm.*, 1894, **33**, 209, 213) who, when discussing the formation of methylpyridinium hydroxide and dimethyl telluride in animals stated " (Es) ist anzunehmen dass die CH_3 Gruppe in den Geweben welche das Vermögen der Methylierung besitzen, als solche vorgebildet ist. . . . Bei Anwesenheit von Pyridin und Tellur käme es zur Methylierung dieser, während normalerweise methylhaltige Stoffe anderer Art, z.B. die Körper der Cholin und der Kreatingruppe entständen." Hofmeister did not mention any particular compound as a possible methyl source. Riesser (*Z. physiol. Chem.*, 1913, **86**, 440) described experiments in which the methyl of betaine and choline was transferred at a high temperature to selenium and tellurium. This work was expanded by Challenger and Higginbottom (*loc. cit.*, 1935) and by Challenger, Taylor, and Taylor (*J.*, 1942, 48).

Between 1939 and 1942 du Vigneaud and his school (see du Vigneaud, " A Trail of Research," Cornell Univ. Press, Ithaca, New York, 1952) provided the first experimental proof that methyl transfer (" transmethylation ") can occur in young white rats, the methyl sources being shown to be choline and methionine. The samples administered contained a high proportion of deuteromethyl groups. Much further work by du Vigneaud, using various methyl sources labelled with ^{14}C or with deuterium or with both, has more clearly defined the mechanism and suggested various intermediate stages.

It is convenient, though not always possible, to distinguish between a methyl " donor " and a methyl " source." It has been rigidly demonstrated that the methyl group of methionine can be transferred intact (du Vigneaud, Cohn, Chandler, Schenck, and Simmonds, *J. Biol. Chem.*, 1941, **140**, 625). In the cases of choline (Simmonds, Cohn, Chandler, and du Vigneaud, *ibid.*, 1943, **149**, 519), betaine (du Vigneaud, Simmonds, Chandler, and Cohn, *ibid.*, 1946, **165**, 639), acetothetin chloride $Cl^-\{Me_2S^+{\cdot}CH_2{\cdot}CO_2H$ (du Vigneaud, Moyer, and Chandler, *ibid.*, 1948, **174**, 477), and dimethyl-β-propiothetin chloride $Cl^-\{Me_2S^+{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ [first isolated from the red alga *Polysiphonia fastigiata*, by one of us and Miss M. I. Simpson (*J.*, 1948, 1591)] (Maw and du Vigneaud, *J. Biol. Chem.*, 1948, **174**, 381, 477; **176**, 1029, 1037; Dubnoff and Borsook, *ibid.*, 1948, **176**, 789) the carbon atom of a methyl group is certainly transferred to homocysteine, giving rise to methionine, but the exact mechanism, which may involve many stages, has not been determined. It is possible that the carbon atom of the methyl group is detached as formaldehyde or formic acid which by reaction with a thiol or an amino-group and subsequent reduction may give rise to SMe or NHMe.

It is fairly clear, however, that the effective fragment is not carbon dioxide (du Vigneaud, Verly, and Wilson, *J. Amer. Chem. Soc.*, 1950, **72**, 2819; Arnstein, *Biochem. J.*, 1951, **48**, 27; Sakami, *J. Biol. Chem.*, 1948, **176**, 995; 1949, **179**, 495) although the elimination of carbon dioxide has frequently been observed during the metabolism of methylthio- and methylamino-derivatives in animals (for references see *Adv. Enzymology*, 1951, **12**, 480).

Sakami (*J. Biol. Chem.*, 1948, **176**, 995; 1949, **179**, 495), du Vigneaud, Verly, and Wilson (*loc. cit.*), and Arnstein (*loc. cit.*) developed the conception of the one-carbon fragment which again brought the formaldehyde hypothesis, or some very similar scheme (see p. 1760), into the foreground as an alternative mechanism for biological methylation. An example may be cited. On administration of glycine, serine, or formate labelled with ^{14}C as shown, $H_2N{\cdot}{}^{14}CH_2{\cdot}CO_2H$, $HO{\cdot}{}^{14}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$, and $H{\cdot}{}^{14}CO_2Na$, the labelled carbon atom appeared in the methyl groups of the choline of the tissues of rats. Reference may also be made to two recent publications in this field by Berg (*J. Biol. Chem.*, 1953, **205**, 145) and Greenberg (*Fed. Proc.*, 1953, **12**, 651).

It follows that true transmethylation involving an intact methyl group is not the only

process concerned in biological methylation. This phenomenon may involve (*a*) true transmethylation, (*b*) transfer of a one-carbon fragment followed by reduction, or (*c*) process (*b*) followed by process (*a*) as the last stage.

Recently we have studied the effect of various potential sources of the methyl group, labelled with ^{14}C, on the production of trimethylarsine and dimethyl selenide in bread cultures of *S. brevicaulis*, and of dimethyl selenide in cultures of *Aspergillus niger* on liquid media or on bread. The sources were choline chloride, betaine, sodium formate, and DL-methionine. Only one methyl group in choline and betaine was labelled. The trimethylarsine and dimethyl selenide were collected as the mercurichlorides $AsMe_3,2HgCl_2$ and $SeMe_2,HgCl_2$, and their radioactivity was measured. The " methylation percentage " was calculated from the ratio

$$\frac{100}{nf} \cdot \frac{\text{Radioactivity of methylated product per mole}}{\text{Radioactivity of methyl source per mole}}$$

where n is the number of methyl groups produced by methylation per molecule of the product and f is the fraction of the total of labelled methyl groups or carbon atoms per molecule which are theoretically labile.

Thus $n = 1$ when the product is $SMeEt,2HgCl_2$; $n = 2$ for $SMe_2,HgCl_2$. The value f is of importance since in choline, betaine, dimethylacetothetin $Me_2S^+\cdot CH_2\cdot CO_2^-$, and dimethyl-β-propiothetin $Me_2S^+\cdot CH_2\cdot CH_2\cdot CO_2^-$ only one methyl group is labile in animals or in tissue preparations (du Vigneaud, Simmonds, Chandler, and Cohn, *J. Biol. Chem.*, 1946, **165**, 639; du Vigneaud, Simmonds, and Cohn, *ibid.*, 1946, **166**, 47; Borsook and Dubnoff, *ibid.*, 1948, **176**, 789; Maw and du Vigneaud, *ibid.*, p. 1037).

The methylation percentage was small with choline chloride, betaine, and sodium formate, varying from 1 to 5, but was very considerable in all experiments with methionine, ranging from 25 to 95. Moreover with methionine a very much smaller proportion of the total ^{14}C is converted into $^{14}CO_2$ than with the other sources.

We have also shown in separate preliminary experiments in cultures of *A. niger* on medium (G) (see p. 1765) that the D- and L- enantiomorphs of $^{14}CH_3$-methionine can both act as methyl donors to selenium to a considerable extent. These results will be described in a forthcoming publication.

It therefore appears that the $^{14}CH_3$ of methionine is transferred intact to arsenic and selenium and that in mycological methylation the part played by this amino-acid is as dominating as in the analogous animal processes. The importance of methionine and formate for transmethylation has also been established for the dimethylamino-group of hordenine in barley seedlings (Kirkwood and Marion, *Canad. J. Chem.*, 1951, **29**, 30; Dubeck and Kirkwood, *J. Biol. Chem.*, 1952, **199**, 307) and the NMe group of nicotine (Brown and Byerrum, *J. Amer. Chem. Soc.*, 1952, 74, 1523). The methyl of the >NMe and methoxyl groups of ricinine of castor beans (Dubeck and Kirkwood, *loc. cit.*) arise from methionine, and the methyl of the methoxyl group of barley lignin is transferred intact from this amino-acid (Byerrum and Flokstra, *Fed. Proc.*, 1952, **11**, 193; Byerrum, Dewey, and Ball, *ibid.*, 1953, **12**, 186).

The dominance of methionine in mould methylation is also suggested by our observations that the methylation percentage for the systems [^{14}C]betaine–selenate and [^{14}C]formate–selenate in bread cultures of *A. niger* under comparable conditions is 2—5 times greater in presence of homocystine than in its absence. This agrees with the observation of Borsook (*J. Biol. Chem.*, 1945, **160**, 635) that homocystine or homocysteine is necessary before the methyl-carbon atom of choline can be transferred to guanidoacetic acid, yielding creatine.

These results suggest that methylation by *S. brevicaulis* and *A. niger* involves a true transmethylation mechanism from methionine which may, however, be produced from homocysteine by acceptance of some other one-carbon fragment, detached from betaine, choline, or formate.

It seems probable, nevertheless, that carbon dioxide is not an intermediate. This follows from a consideration of the " CO_2 ratio " which is obtained by dividing the specific activity of the carbon dioxide evolved from the cultures by the specific activity of the

methylated product per carbon atom (see Tables 1, 2, and 5). If radioactive carbon dioxide arising from the labelled sources by mycological oxidation is in equilibrium within the cell with the carbon dioxide evolved by the normal metabolism of the mould this ratio must be at least unity if carbon dioxide is an intermediate. Except in the case of *A. niger* and sodium formate this ratio was always fractional, and with methionine as methyl source was extremely low.

There is much evidence from animal metabolism to show that carbon dioxide is not a source of the methyl group (du Vigneaud, *J. Amer. Chem. Soc.*, 1950, **72**, 2819; Arnstein, *loc. cit.*). Ressler, Rachele, and du Vigneaud (*J. Biol. Chem.*, 1952, **197**, 1) showed by the use of [^{14}C,α-D]formic acid, D·$^{14}CO_2H$, that no oxidation of the non-carboxylic hydrogen atom of formate occurs during synthesis of choline-methyl groups in the rat, thus excluding carbon dioxide as a possible precursor of the methyl group. Kirkwood and Marion (*loc. cit.*) reached similar conclusions from their work on hordenine formation in barley seedlings.

Methylation of sulphur by [^{14}C]choline and [^{14}C]formate has also been detected in bread cultures of *S. brevicaulis* containing diethyl disulphide or *S*-ethylcysteine. Fission of the S–S (Challenger and Rawlings, *J.*, 1937, 868; Blackburn and Challenger, *J.*, 1938, 1872) and S–C linkages (Challenger and Charlton, *J.*, 1947, 424) produces ethanethiol [detected as non-radioactive $(EtS)_2Hg$] and radioactive ethyl methyl sulphide (detected and counted as the mercurichloride).

It is seen from Tables 2, 5, and 7 that the percentage methylation of selenium is much greater in cultures of *A. niger* on a liquid medium (G) containing sucrose, inorganic salts, glycine, and DL-methionine than when this organism or *S. brevicaulis* is grown on bread. This we attribute to the dilution effect of the methionine in the protein of the bread. A similar explanation may account for the much lower methylation figure observed when non-radioactive methionine methiodide is added to *A. niger* cultures on medium (G) containing [^{14}C]methionine and selenate (Table 8). Presumably methionine is produced by demethylation of the methiodide and dilutes the radioactive methionine.

Another reaction, however, occurs here—fission of the methiodide to dimethyl sulphide—a decomposition observed by Challenger and Charlton (*loc. cit.*) using bread cultures of *S. brevicaulis* and by Challenger and Liu (*Rec. Trav. chim.*, 1950, **69**, 334) with *Penicillium notatum* on both liquid and bread media. We have shown, however, (see p. 1770), that this is not the cause of the low activity of the dimethyl selenide mercurichloride.

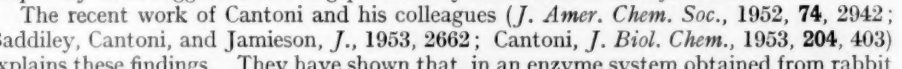
In the experiments with sodium selenate the purity of the dimethyl selenide mercurichloride was checked by m. p., often by mixed m. p. (Challenger and North, *J.*, 1934, 68), and in several cases by recrystallisation without alteration in specific activity. In one case crystallisation from aqueous mercuric chloride lowered the activity (owing to partial conversion into a higher mercurichloride, see p. 1770), but on decomposition with sodium hydroxide and re-absorption in mercuric chloride the original activity was observed. It appeared conceivable that part of the radioactivity of the trimethylarsine and dimethyl selenide mercurichlorides might be due to a mercuric chloride compound of an alkylamine or alkylamine salt arising through mycological fission of the carbon–nitrogen link in choline or betaine. This possibility was eliminated when it was shown that the hydrochlorides of methylamine, diethylamine, and trimethylamine gave no precipitate in either acidified or neutral mercuric chloride. No evidence for such a C–N fission was obtained by Challenger and Higginbottom with betaine in cultures of *S. brevicaulis* on a modified Czapek–Dox medium (*Biochem. J.*, 1935, **29**, 1768), or by us in cultures of *A. niger* on bread (see p. 1769).

In the experiments where methionine was used as a methyl donor it seemed possible that complications due to subsidiary reactions might arise. *S. brevicaulis* in bread cultures containing the *S*-alkylcysteines gives alkanethiol and alkyl methyl sulphide (see p. 1760). This action is exerted to a much smaller extent on methionine, especially in liquid media. With *A. niger* Challenger and Charlton (*loc. cit.*) observed only a slight thiol or sulphide odour in bread cultures containing 0·5% of DL-methionine. Nevertheless, when using this amino-acid labelled in the methyl group with ^{14}C, radioactive methanethiol, dimethyl sulphide, and traces of dimethyl disulphide (from oxidation of the thiol) might be evolved. Contamination of the precipitated dimethyl selenide and trimethylarsine mercurichlorides

must therefore be avoided. The methanethiol is not a danger, as it is completely removed by mercuric cyanide. In no case were more than traces of its mercury derivative observed. Dimethyl sulphide, the amount of which is usually roughly equivalent to that of methanethiol, yields a mercurichloride which is rather unstable in Biginelli's solution (mercuric chloride in hydrochloric acid, *J.*, 1933, 99) and most of it would pass on and be absorbed in the third reagent, neutral mercuric chloride, giving $2SMe_2,3HgCl_2$. Any disulphide would give a precipitate of the formula $MeS{\cdot}HgCl,xHgCl_2$ in this reagent (Blackburn and Challenger, *J.*, 1938, 1874) which could therefore deposit a mixture containing traces of these two sulphur compounds as well as dimethyl selenide mercurichloride, $SeMe_2,HgCl_2$. On treatment of the precipitate with sodium hydroxide and aspiration afresh into acid mercuric chloride, however, only the dialkyl selenide and sulphide volatilise and again most of the dimethyl sulphide would pass through the Biginelli's solution. This is indicated by Experiment 3, Table 8, and in Table 9, where the *A. niger* cultures contained, in addition to selenate and [^{14}C]methionine, inactive dimethyl-β-propiothetin bromide which with *S. brevicaulis* on bread yields only about 3% of dimethyl sulphide (Challenger and Liu, *loc. cit.*) but in liquid cultures of *A. niger* produces considerable quantities. Here the methylation percentage and m. p. observed with the first deposit are very low, owing to contamination with inactive dimethyl sulphide mercurichloride. Repeated decomposition with alkali and slow aspiration afresh into acid mercuric chloride raise the m. p. considerably and the methylation percentage then agrees with that obtained in other experiments, where only traces of dimethyl sulphide could have been produced.

This suggests that, in comparison with methionine, dimethyl-β-propiothetin bromide is negligible as a direct methyl-donor, otherwise a dilution effect would have been observed at constant activity. A similar result was obtained with dimethylacetothetin chloride, except that this does not yield dimethyl sulphide in mould cultures (Challenger and Liu, *loc. cit.*). The same conclusion may be reached in the case of betaine where no dilution effect was detected with selenate in *A. niger* cultures (Table 8). It may appear surprising that these 'onium compounds, including the methylmethioninesulphonium ion are so much inferior to methionine as methyl sources, especially as a methylated 'onium structure has frequently been suggested as being particularly suitable as a methyl source.

The recent work of Cantoni and his colleagues (*J. Amer. Chem. Soc.*, 1952, **74**, 2942; Baddiley, Cantoni, and Jamieson, *J.*, 1953, 2662; Cantoni, *J. Biol. Chem.*, 1953, **204**, 403) explains these findings. They have shown that, in an enzyme system obtained from rabbit liver and containing adenosine triphosphate, methionine yields orthophosphoric acid and an " active methionine " which they regard as responsible for transmethylation to guanidinoacetic acid, nicotinamide, and dimethylaminoethanol, giving creatine, *N*-methylnicotinamide, and choline respectively. To this compound they assign the annexed quaternary



structure. It is possible, therefore, that this complex—the *S*-adenosylmethionine ion—is concerned also in the transfer of the methionine-methyl group to arsenic or selenium in mycological methylation. If so it is obvious that the simple methylsulphonium derivative of methionine cannot enter into such a combination unless it first loses a methyl group to form methionine and that methionine is therefore a more effective methyl source than its own methylsulphonium derivative or, probably, any other simple 'onium compound.

Experimental

The radioactive choline was prepared by interaction (in a vacuum-train cooled by liquid air) of [^{14}C]methyl iodide with dimethylaminoethanol (Ferger and du Vigneaud, *J. Biol. Chem.*, 1950, **185**, 53.) The labelled choline iodide was converted into the chloride which was then diluted with inactive chloride (Found, for the corresponding picrate: C, 42·6; H, 10·5. Calc. for $C_{11}H_{16}O_8N_4$: C, 43·0; H, 10·1%). It showed 637·7 counts per minute (c.p.m.), *i.e.*, 212,000 c.p.m. per mmole. The activity was 308×10^{-6} μc per mg. by comparison with a sample of the picrate standardised by the Atomic Energy Research Establishment, Harwell. The activity calculated as choline chloride was $102{\cdot}2 \times 10^{-3}$ μc per mmole. The choline chloride was oxidised to betaine in 86% yield by potassium permanganate in very dilute, slightly acid solution (Lintzel and Fomin, *Biochem. Z.*, 1931, **238**, 438). The radioactive betaine was converted into the hydro-

chloride, m. p. 238° (Found: C, 39·0; H, 7·6; Cl, 22·9. Calc. for $C_5H_{12}O_2NCl$: C, 39·1; H, 7·9; Cl, 23·1%). Its activity was $102·2 \times 10^{-3}$ μc per mmole. It was converted into the picrate, m. p. 184°, which gave 614·5 c.p.m., *i.e.*, 213,000 c.p.m. per mmole. This shows that the plating method described below gives consistent results.

Radioactive sodium formate was diluted with " AnalaR " material by dissolution in water and evaporation to dryness *in vacuo* over phosphoric oxide. Titration with neutral potassium permanganate gave: equiv., 67·6 (Calc.: 68·0). The specific activity was: $126·5 \times 10^{-3}$ μc per mmole.

Radioactive methionine was prepared from *S*-benzylhomocysteine, sodium, and [^{14}C]methyl iodide in liquid ammonia (Melville, Rachele, and Keller, *J. Biol. Chem.*, 1947, **169**, 419) and finally diluted to a convenient activity. Dissolution of *S*-benzylhomocysteine in ammonia and interaction with sodium were facilitated by stirring with a stream of pure hydrogen. Sodium wire was added until a blue colour persisting for 10 min. was produced. (When carefully dried nitrogen, from a cylinder, was used as a stirrer no permanent blue colour could be obtained regardless of the amount of sodium added. This was attributed to the effect of traces of oxygen in the nitrogen.) The colour was then discharged by careful addition of inactive methyl iodide. The [^{14}C]methyl iodide, warmed to 50°, was then introduced in a stream of hydrogen. Inactive methyl iodide was then added till the ammonia solution no longer gave a positive nitroprusside reaction for the thiol group. Any radioactive methionine remaining in the mother-liquors after crystallisation of the final product was removed by addition of the non-active amino-acid and separated as described by Melville *et al.* (*loc. cit.*). On the second operation the isolated methionine had only a low radioactivity. The united fractions were then crystallised from aqueous alcohol and dried *in vacuo* over phosphoric oxide (radioactive yield 48%). Paper-chromatography with 80% phenol or butanol–acetic acid–water as the moving phase gave two spots with ninhydrin, due to methionine and its sulphoxide. The sulphoxide is known to be produced by oxidation of methionine on the filter-paper during the chromatographic process (Dent, *Biochem. J.*, 1948, **43**, 169). The methionine was analysed (Found: C, 40·3; H, 7·3; N, 9·0; S, 21·1. Calc. for $C_5H_{11}O_2NS$: C, 40·25; H, 7·45; N, 9·4; S, 21·5%); its specific activity was 356×10^{-3} μc per mole. The radioactive sodium formate and methyl iodide were obtained from the Radiochemical Centre, Amersham.

Optically active methionines were prepared by resolution of DL-homocystine obtained from DL-methionine and sulphuric acid (Butz and du Vigneaud, *J. Biol. Chem.*, 1932, **99**, 135). *S*-Benzyl-*N*-formylhomocysteine was resolved by brucine (du Vigneaud and Patterson, *ibid.*, 1935, **109**, 97) and after removal of the formyl and benzyl groups was converted into methionine with [^{14}C]methyl iodide. The radioactive D- and L-methionine had $[\alpha]_D^{20}$ +7·75° and −7·6° in 1% aqueous solution. Du Vigneaud and Patterson (*loc. cit.*) give $[\alpha]_D^{25}$ +8·0° and −7·7°. Windus and Marvel (*J. Amer. Chem. Soc.*, 1930, **52**, 2675) give $[\alpha]_D^{25}$ +8·7° and −8·1°. The purity of both isomers was checked as in the case of DL-methionine by paper chromatography. Two spots were obtained as before. Activities were for D-methionine 725×10^{-3} and for L-methionine 1440×10^{-3} μc per mmole.

Culture Media.—(a) *Solid.* Bread crumbs (150 g.) and distilled water (25 c.c.) were sterilised in 1-l. conical flasks plugged with cotton wool for 25 min. at 15 lb. pressure.

(b) *Liquid.* A modified Czapek–Dox medium was prepared from sodium nitrate (2·0 g.), potassium chloride (0·5 g.), magnesium sulphate (0·5 g.), ferrous sulphate (0·01 g.), and potassium dihydrogen phosphate (1·0 g.) in water (1 l.). The medium (300 c.c.) with 10% of sucrose and 0·25% (10 mmole) of glycine was sterilised as before in 1·5-l. conical flasks and designated Medium G.

Cultivation of Organisms and Addition of Substrates.—Two moulds were used: (1) *Scopulariopsis brevicaulis*, strain Washington 2, N.C. Type Cultures No. 580 (designated Strain D by Challenger, Higginbottom, and Ellis, *J.*, 1933, 98), was used only on bread medium, which was heavily inoculated from a sub-culture on a potato–agar slope. Incubation was usually at 35° for 4—5 days followed by a similar period at room temperature. (2) *Aspergillus niger*, strain No. 17, obtained from Dr. T. K. Walker of the Manchester College of Technology, was sub-cultured on wort–agar slopes. When grown on sterile bread the cultures were incubated for 2 days at 35° and 1—2 days at room temperature, growth and sporing being more rapid than with *S. brevicaulis*. The Medium G after inoculation with *A. niger* was incubated at 35° for 2—3 days and left at room temperature for a similar time, to yield a thin, even, lightly sporing mycelial pad. Too vigorous growth is disadvantageous. The substrates and methyl sources, if stable, were sterilised as before. Radioactive materials were usually sterilised in separate tubes, each containing 15 c.c. of water, which was then added to the cultures. Arsenious oxide

or sodium selenate solutions were sterilised in bulk and added by sterile pipette. Compounds unstable to heat were sterilised in aqueous solution by Seitz filtration and added from the graduated vacuum-receiver.

After addition of the materials to the cultures the cotton-wool plugs were replaced by two-hole rubber bungs fitted with sterilised inlet and outlet tubes loosely plugged with cotton wool. The flasks (usually two or three) were then connected in series, and volatile matter was removed by a slow stream of air which was freed from carbon dioxide and any traces of aliphatic sulphides or selenides which might be present in the laboratory air by previous passage through 2N-sodium hydroxide, 3% mercuric chloride, and sterile cotton wool. On issuing from the cultures the air passed through a series of selective reagents : (*a*) aqueous mercuric cyanide which removed hydrogen sulphide, thiols, and selenothiols—only in special cases were these present; (*b*) acid mercuric chloride which removed trimethylarsine as the dimercurichloride, and most of the dimethyl selenide as the mercurichloride; (*c*) neutral mercuric chloride which absorbed the remainder of the dimethyl selenide, together with dialkyl sulphides and disulphides; (*d*) two flasks of aqueous potassium hydroxide (10—15%), containing phenolphthalein, which absorbed carbon dioxide. When the original colourless solution became pink a fresh flask was employed. The carbon dioxide was then estimated volumetrically.

Purification of End-products for Counting.—Carbon dioxide was precipitated as barium carbonate by addition of barium chloride to the 10—15% potassium hydroxide solution used as absorbent, separated in a centrifuge, washed with water, and dried at 100°. The trimethylarsine and dimethyl selenide, which were known to be pure (*J.*, 1933, 95; 1934, 68; *Biochem. J.*, 1948, **43**, 78), were precipitated as the mercurichlorides. It was, therefore, considered unnecessary to recrystallise these compounds to constant activity in every case, though this was often done when using dimethyl selenide mercurichloride. Contamination with a higher or lower mercurichloride would affect the specific activity and this factor has been investigated for dimethyl selenide (Table 10). The object of the work was to compare the effectiveness of various methyl sources and rather less stress has been laid on obtaining an accurate value for the specific activity of each deposit. The results are, however, comparable and repeatable.

In some experiments (see p. 1769) it seemed possible that traces of dimethyl sulphide might contaminate the dimethyl selenide. In a few cases its presence was definitely established. Consequently the mercurichloride was treated with aqueous sodium hydroxide, and the liberated selenide and sulphide were removed in a stream of purified air. Passage through (*a*) mercuric cyanide and (*b*) acidified and (*c*) neutral mercuric chloride as before gave no precipitate in (*a*), while dimethyl selenide collected as the mercurichloride in (*b*) and any dimethyl sulphide was precipitated in (*c*). When only traces of the sulphide were present the aspiration was usually continued for 14 hr., so as to remove all sulphide from (*b*). With larger quantities (see Table 9) the process was repeated several times with the precipitate in (*b*). The purity of the deposits was checked by m. p. and often by mixed m. p. determinations.

Details of Radioactive Assay.—The active barium carbonate, sodium formate, methionine, and choline and betaine picrates were spread evenly in a circular depression in a " Perspex " disc (2·55 sq. cm.) and compacted with a close-fitting chromium plated metal plunger. The mercurichlorides adhered to the metal and could not be treated in this way. The " Perspex " discs were perforated, fitted with a filter paper, and made the base of a cylindrical funnel. This was half-filled with water, the mercurichloride added as a fine aqueous suspension, and gentle suction applied. The uniform layer so formed was dried in air. The weight of material on the plates was wherever possible greater than 0·07—0·08 g., the minimum weight required to obtain a deposit of " infinite thickness " with the particular discs used. This was determined by recognised procedure, with choline picrate as standard.

Other active materials were also compared with this standard, but normally absolute values in μc per mmole were not required because the methylation percentage (see p. 1762) was usually calculated by direct comparison of the c.p.m. of the product and the methyl source. Specimens were dried by 15 minutes' air-suction, followed by 2—3 hours' storage in a vacuum-desiccator. A thin end-window Geiger–Müller counter, " lead castle," Standard H.T. scaler, and probe units were used.

Counting and calculation of errors were carried out as described by Fisher (" Statistical Methods for Research Workers," Oliver and Boyd, Edinburgh, 1950) and by Kamen (" Radioactive Tracers in Biology," 2nd Ed., Academic Press, New York, 1950). Counting errors are quoted only where they are of approximately the same order of magnitude as the observed figures, as, *e.g.*, in Table 6. The effect of " back-scatter " due to the heavy mercury atoms was neglected and may render all methylation percentages 6—10% high (Dransfield and

Challenger, unpublished work) but this factor will be constant, and since all calculations of methylation percentage are based on mercurichlorides the results will be strictly comparable.

" Biological " errors arising from variations in intensity of inoculation, rate of growth, or rate of metabolism are difficult to assess but the results were reproducible. Controls were set up wherever necessary.

Results.—Results are shown in Tables, to which the following notes are added.

TABLE 1.

Mould : *S. brevicaulis*, Washington 2.
Medium : Bread, 150 g. per flask.
Substrate : Arsenious oxide, 0·25 mmole per flask.
Trimethylarsine collected and counted as $AsMe_3,2HgCl_2$.

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2	CO_2 ratio
[*Me*-^{14}C]Choline chloride	1	14	1·9	968	—	—
[*Me*-^{14}C]Betaine	1	21	0·7	2900	—	—
Na [^{14}C]formate	5	14	3·1	2035	71	0·18
DL-[*Me*-^{14}C]Methionine ...	1	5	28·3	450	0·3	0·00008
		15	13·5	488	0·4	

Table 1. The m. p. of the five deposits of trimethylarsine dimercurichloride were respectively 265°, 263—265°, 262—264°, 261—263° (mixed m. p. 261—263°), and 262° (mixed m. p. 261—262°) (all with decomp.). Challenger, Higginbottom, and Ellis (*loc. cit.*) give m. p. 265° (decomp.). The yields of the mercurichloride varied from 9 to 18%. Addition of methionine does not affect the yield (see Tables 3 and 6). Unpublished work by Dr. Marjorie L. Bird showed that, in similar experiments without addition of any methyl source, after more than a year's aspiration the yield of trimethylarsine calculated on the arsenious oxide was only about 85%.

TABLE 2.

Mould : *S. brevicaulis*, Washington 2.
Medium : Bread, 150 g. per flask.
Substrate : Sodium selenate, 2·5 mmole per flask.
Dimethyl selenide collected and counted as $SeMe_2,HgCl_2$.

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2	CO_2 ratio
[*Me*-^{14}C]Choline chloride	1·0	14	1·2	1080	—	—
	5·0	7	4·1	1240	47	0·3
		14	3·1			
[*Me*-^{14}C]Betaine	1·0	14	1·1	1260	—	—
	5·0	7	4·0	1230	43	0·3
		14	2·3			
Na [^{14}C]formate	(1) 5·0	14	4·4	1288	100 ± 10	0·2
	(2) 5·0	1·5	—	346	57	
		5 [a]	5·8	441	10	
		7	3·0	422	4·7	
		9	2·7	335	2·5	
		14	0·9	513	1	
DL-[*Me*-^{14}C]Methionine ...	1·0	4 [b]	25·5	351	0·15	0·00005
		15 [c]	12	582	0·8	

Table 2. On three occasions the m. p. of the mercurichloride was taken : (*a*) 152—154°, (*b*) 152—154° and mixed m. p. 153—154°, (*c*) m. p. and mixed m. p. 152—153°. Dimethyl selenide mercurichloride has m. p. 153—154° (Challenger and North, *loc. cit.*). The yield averaged 11% except when methionine was present, the figure then being 6%. Other examples of this effect are mentioned in Tables 3 and 6.

TABLE 3.

Mould : *S. brevicaulis*, Washington 2.
Medium : Bread, 150 g. per flask
Substrate : Diethyl disulphide, 4·1 mmole per flask.
Methyl ethyl sulphide collected and counted as $SMeEt,2HgCl_2$.

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2
[*Me*-^{14}C]Choline chloride	3·6	7	2·4	980	24·2
Na [C^{14}]formate	3·6	3	6·5	360	55
		6	4·8	490	13·5
		9	—	350	7
		12	—	380	3

Table 3. The m. p. of the ethyl methyl sulphide mercurichloride was 125—126°. Challenger and Rawlings (*J.*, 1937, 868) give m. p. 127—128°. The yields were 7·5—8·5%, calc. on the disulphide.

TABLE 4.

Substrate : *S*-Ethylcysteine, 1·66 mmole per flask. Other conditions as in Table 3. Yield of mercurichloride, 8%.

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2
[*Me*-^{14}C]Choline chloride	3·6	12	0·8	2180	38·7
Na [^{14}C]formate	3·6 *	9	8·1	470	89

* Very slow aspiration.

TABLE 5.

Mould : *A. niger* 17.
Medium : Bread, 150 g. per flask. Here, and in Tables 6—8 the substrate was sodium selenate (2·5 mmole per flask) and the dimethyl selenide was collected and counted as $SeMe_2,HgCl_2$.

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2	CO_2 ratio
[*Me*-^{14}C]Choline chloride	5·0	3	0·1	300	1	0·5
		11	1·0	300	5	
[*Me*-^{14}C]Betaine	5·0	5	1·1	340	3·6	—
		10	5·3	470	9·8	0·1
		19	1·8	400	4·0	
Na [^{14}C]formate	5·0	3	2·0	410	37	—
		11	0·9	370	25	0·9
DL-[*Me*-^{14}C]Methionine ...	5·0	7	44	600	0·3	0·0001
		14	—	550	0·4	
		25	40	268	0·1	
		42	33·5	925	1·0	

Table 5. The m. p. of the dimethyl selenide mercurichloride varied from 152—154° to 153—154° (mixed m. p. 153—154°). Yields of $SeMe_2$ produced averaged 24%, except in presence of methionine (yield 7%, see Tables 3 and 7).

TABLE 6. *Effect of adding homocystine.*

Mould : *A. niger* 17. Medium : Bread, 150 g. per flask.

Days of aspirn.	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2	Days of aspirn.	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2
	Homocystine, 1·25 *mmole.* [*Me*-^{14}C]*Betaine*, 5·0 *mmole.*				[*Me*-^{14}C]*Betaine only.*		
3	5·1 ± 0·3	—	—	3	2·5 ± 0·2	730	26·5
6	7·8 ± 0·2	780	44·6	6	1·6 ± 0·15	—	—
15	7·4 ± 0·2	1450	43·4	15	5·2 ± 0·3	1370	29·7
	Homocystine, 1·25 *mmole.* *Sodium* [^{14}C]*formate*, 5·0 *mmole.*				*Sodium* [^{14}C]*formate only.*		
3	3·2 ± 0·1	550	79·8	3	1·9 ± 0·1	570	71·5
6	1·4 ± 0·07	550	11·5	6	0·45 ± 0·05	1070	16·4
9	0·52 ± 0·05	1700	8·9	9	0·15 ± 0·03	1640	11·8
15	0·25 ± 0·04	—	—	15	0·11 ± 0·02	—	—
	Homocystine, 1·25 *mmole.* [*Me*-^{14}C]*Choline chloride*, 3·0 *mmole.*				[*Me*-^{14}C]*Choline chloride only.*		
3	1·8	1050	30	3	0·8	900	6
6	3·0	—	—	6	4·3	—	—
9	4·5	940	17	9	2·0	960	25
13	3·3	—	—	13	6·7	—	—
19	2·9	830	7	19	6·3	910	7·5

Table 6. M. p.s of $SeMe_2,HgCl_2$ were 152—153°. The average yield of $SeMe_2$ over 14 days was 46% in absence, and 45% in presence, of homocystine.

The results of experiments without homocysteine, where formate or betaine was used as methyl source, compared quite well with those of similar experiments given in Table 5. The marked increase in the percentage methylation when homocystine is also present is discussed on

p. 1762. When choline is used as the methyl source, however, there are marked differences. The results in Table 5 suggest that, unlike *S. brevicaulis*, *A. niger* cannot utilise choline so readily as betaine. The results in Table 6 for choline with or without homocystine show, however, that the percentage methylation, although initially less than that for betaine, is ultimately about the same. The only known difference in conditions between the two sets of experiments is that in the case of those in experiments of Table 6 air was passed over the cultures faster than in those of Table 5. Thus it appears that the utilisation of choline as a methyl source for *A. niger* depends largely on an oxidation process. This is in agreement with animal experiments, where choline is said only to be effective as a methyl source if choline oxidase is present. It is suggested that the choline is first oxidised to betaine before the methyl group is available for methylation (Dubnoff, *Fed. Proc.*, 1949, **8**, 195; *Arch. Biochem.*, 1949, **24**, 251; Muntz, *J. Biol. Chem.*, 1950, **182**, 489; Soloway and Stetten, *ibid.*, 1953, **204**, 207).

Neither trimethylamine nor ammonia is evolved from choline chloride in bread cultures of *A. niger*. When a tube containing dilute hydrochloric acid was inserted before the mercury salts in the absorption train, and the acid finally evaporated, no residue was obtained.

TABLE 7.

Mould: *A. niger* 17. Medium G (300 c.c. per flask).

Methyl source	Concn. (mmole per flask)	Days of aspiration	Methylation (%)	CO_2 (mmole)	Activity (%) recovd. as CO_2
[*Me*-^{14}C]Betaine	2·0	11	11·1	—	—
		22	19·6	948	22·1
		40	22·6		
DL-[*Me*-^{14}C]Methionine ...	* 2·0	16	96	1190	16
		42	55·4		
	2·0	10	95·2		
		26	86·6	1420	16
		41	13·3	170	13·9
		50	3·2		

* Here the liquid medium contained ammonium nitrate (0·5%) instead of the usual glycine (0·25%). These cultures did not spore, but a good even pad of white mycelium was formed in 4 days. They appeared to produce dimethyl selenide only half as rapidly as those grown on medium G.

Table 7. The $SeMe_2,HgCl_2$ had m. p. and mixed m. p. 152—153°. Yields of $SeMe_2$ from selenate were here more difficult to assess owing to loss in the purification. They were of the order of 10% in 28 days, except in the [*Me*-^{14}C]betaine experiment without added methionine, where the yield was of the order of 20%.

Table 8. M.p.s and mixed m. p.s for $SeMe_2,HgCl_2$ were 152—153°.

TABLE 8. *Competition experiments.*

Mould: *A. niger* 17. Culture: Medium G.

Methyl source	Concn. (mmole per flask)	Aspirn. (days)	Methyln. (%)
[*Me*-^{14}C]methionine (2 mmole per flask) plus:			
Betaine	5·0	16	99
		31	79
Dimethylacetothetin chloride	5·0	13	98
		28	80·5
Dimethyl-β-propiothetin bromide *	5·0	13	94·5
		28	82
S-Methyl-DL-methioninesulphonium iodide *	5·0	28	59

* These cultures also produced *ca.* 15 and 20% respectively of inactive dimethyl sulphide. This was separated from active dimethyl selenide as described on p. 1766. The dimethyl sulphide was roughly determined from the weight of mercurichloride $2SMe_2,3HgCl_2$ obtained after separation.

Examination of Radioactive Mercurichlorides.—Radioactive specimens of $SeMe_2,HgCl_2$ collected from several experiments with DL-methionine as methyl donor were diluted with an inactive sample, giving specimen (A), m. p. 152—153°; this was recrystallised from aqueous 3% mercuric chloride, giving (B), m. p. 156—157°, and finally decomposed with sodium hydroxide; the dimethyl selenide was again absorbed in Biginelli's solution, giving specimen (C), m. p. 152—153°. The three samples were assayed. The c.p.m. were 77, 49, and 79 respectively. The experiment provides further evidence that constant activity had been attained for sample (A) of dimethyl selenide mercurichloride. Sample (B) presumably contained some mercurichloride containing a larger proportion of mercury. Further evidence for the formation of this

was furnished in the first experiment in Table 7 where the original deposit (m. p. 154—155°) in neutral mercuric chloride gave 79 c.p.m.; on purification by aspiration as usual the m. p. fell to 152—153° and the c.p.m. rose to 98. See also Table 10.

Slight traces (5—10 mg.) of $(MeS)_2Hg,Hg(CN)_2$, m. p. 138—139° (see p. 1760; cf. Briscoe, unpublished work), are normally produced in experiments with *A. niger* on medium G containing selenate and methionine. A somewhat larger amount (about 25 mg.) was, however, produced in the experiment with selenate + [*Me*-^{14}C]methionine + betaine (Table 8), and, as would be expected, was found to be radioactive. Its specific activity per methyl-C atom was 98% of that of the methionine added to the culture. The experiment with DL-[^{14}C]methionine + *S*-methyl-DL-methioninesulphonium iodide + selenate was of particular interest because here 80 mg. of this compound were produced. Although its m. p. and mixed m. p. were identical with the corresponding figures for the 25-mg. specimen, the specific activity per C atom was only 63% of that of the radioactive methionine added, instead of the expected 98%. It is interesting that here there was also a dilution in the radioactivity of the dimethyl selenide from the usual figure of about 90% to 59%. This dilution could be wholly or partly due to direct methylation by the non-radioactive methylmethioninesulphonium iodide. It seems more likely, however, since non-radioactive methanethiol is certainly produced, that the methylmethioninesulphonium iodide has lost a methyl group, to yield non-radioactive methionine. This then undergoes S–C fission along with the radioactive methionine already present, to yield the " diluted " methanethiol. This non-radioactive methionine so produced would also itself methylate the selenium. It was shown by Challenger and Charlton (*J.*, 1947, 429; *Ann. Reports*, 1946, **43**, 262) and by Challenger and Liu (*loc. cit.*) that methylmethioninesulphonium iodide itself undergoes fission in cultures of *S. brevicaulis* and *Penicillium notatum*, yielding dimethyl suphide but no methanethiol. The conditions, however, differed considerably from those of the experiments summarised in Table 8, in that neither selenate nor added methionine was present.

In view of the importance of *S*-adenosylmethionine (see p. 1764) in biological methylation it is possible that the methylsulphonium iodide of methionine must be converted into methionine before transmethylation to selenium can take place. In that case, the methyl group necessarily removed may be captured by homocysteine, giving rise to more methionine. Oxidation to carbon dioxide would appear to be inconsiderable, judging from the results of an experiment with radioactive methylmethioninesulphonium iodide (unpublished work).

Separation of the Mercurichlorides of Dimethyl Sulphide and Dimethyl Selenide.—Table 9 illustrates the gradual separation, as shown by activity and m. p., in experiment 3 of Table 8.

TABLE 9.

No. of aspiration	Time of aspiration (hr.)	Wt. (mg.) of ppt. in acid $HgCl_2$ soln.	" % Methylation " as $SeMe_2$	M. p.
1	1	240	25	147—148°
2	5	75	65	150—151
3 *	14	40	88	152—153
4	14	30 *	89	152—153
5	14	90 †	94·5	152—153

* These weights were inconveniently low and were corrected to infinite thickness. † Check on infinite thickness correction by dilution with inactive $SeMe_2,HgCl_2$ and aspiration as before.

The original deposit was decomposed with sodium hydroxide, and the dimethyl selenide and sulphide were volatilised in an air-stream through (*a*) acid and (*b*) neutral mercuric chloride. After 1 hr. (aspiration 1) the deposit in (*a*) was 240 mg. This was again made alkaline, and the operation repeated (aspiration 2), and so on.

Further Investigation of the Higher Mercurichloride of Dimethyl Selenide.—Radioactive dimethyl selenide monomercurichloride collected from various absorption trains attached to mould cultures was made alkaline and the liberated dimethyl selenide separately aspirated into 20 c.c. of each of the mercuric chloride solutions shown in column 1 of Table 10, so that approx.

TABLE 10.

Reagent	C.p.m. of $SeMe_2$ derivative	M. p. of $SeMe_2$ derivative	" Fractional activity of maximum "
(1) Biginelli's solution (10% $HgCl_2$ in 2N-HCl)	1450	152—153°	1·00
(2) 3% Aq. $HgCl_2$	1139	154—155	0·78
(3) 5% Aq. $HgCl_2$ (*a*)	1096	155—156	0·75
(*b*) after washing of ppt. with water	1384	153—154	0·95
(4) 10% Ethanolic $HgCl_2$	1455	152—153	1·00

0·1 g. of solid collected in each reagent. These deposits were suspended in about 5 c.c. of water, quickly filtered on to the standard discs, and counted. The deposit from (3) was then replaced in the filtration apparatus and repeatedly washed with water (6 × 10 c.c.). The activity and m. p. of this precipitate (3*b*) were then determined.

It is seen that with neutral aqueous mercuric chloride (2) and (3*a*) the activity declined and the m. p. rose, compared with (1) and (4) where m. p. and activity are the same. The precipitate formed in (1) is known to be $SeMe_2,HgCl_2$ (Challenger and North, *J.*, 1934, **70**; North, Thesis, Leeds, 1934), and that in (4) must be the same. In precipitates in (2) and (3*a*) extra mercuric chloride must be attached to the dimethyl selenide molecule. The composition $2SeMe_2,3HgCl_2$ is suggested for this complex by the figures in column 4. These ratios represent the c.p.m. of the sample divided by the maximum c.p.m. obtained (*i.e.*, for sample 4). Since the activity of the dimethyl selenide is the same in every case this ratio will be invariably proportional to the ratio of the molecular weights of the mercuric chloride complexes. The " fractional activity of maximum " for $2SeMe_2,3HgCl_2$ would be $381/516{\cdot}5 = 0{\cdot}74$, which is very near to the value obtained for the precipitate in (3). The extra mercuric chloride must be loosely attached because washing with water removes most of it, and the m. p. and c.p.m. then approximate to those of the monomercurichloride. It should be noted that the higher mercurichloride is formed in the aqueous, less concentrated mercuric chloride solutions. In acidic and alcoholic solutions the greater solubility of mercuric chloride presumably favours the formation of the lower derivative. It may be mentioned that dimethyl sulphide mercurichloride has the composition $2SMe_2,3HgCl_2$ (for references see Blackburn and Challenger, *J.*, 1938, 1878) and that ethyl methyl selenide forms a stable dimercurichloride, m. p. 141·5°, and a monomercurichloride, m. p. 100°, which loses ethyl methyl selenide in air with rise in the m. p. This monomercurichloride forms the derivative with more mercury on recrystallisation from 3% aqueous mercuric chloride (Bird and Challenger, *J.*, 1942, 573).

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The cis- *and* trans-2-*Benzyl*cyclo*hexanols: The Reduction of* 2-*Benzylidene- and* 2-*Benzyl*-cyclo*hexanones.*

By PETER B. RUSSELL.

[Reprint Order No. 4943.]

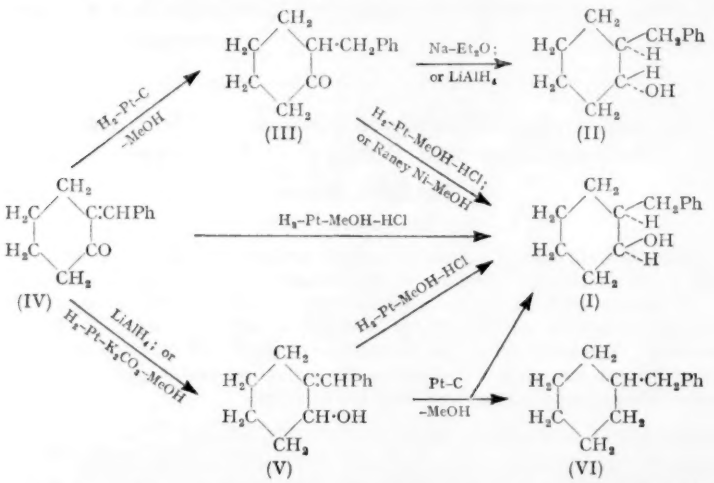
On the basis of evidence already available the known 2-benzyl*cyclo*hexanol of m. p. 77° is assigned the *trans*-configuration following the generalizations of von Auwers and Skita. *cis*-2-Benzyl*cyclo*hexanol has been prepared by catalytic reduction of 2-benzyl*cyclo*hexanone with platinum in acidic methanol. The steric effects of platinum and platinized charcoal catalysts and of lithium aluminium hydride in the reduction of this ketone and of 2-benzylidene*cyclo*hexanone have been investigated.

2-BENZYL*cyclo*HEXANOL can exist in two racemic forms, *viz.*, *cis* (I) and *trans* (II). However, only one of these (m. p. 77°; 3 : 5-dinitrobenzoate, m. p. 133—135°) has been described. This was prepared by reduction of 2-benzyl*cyclo*hexanone (III) with sodium in moist ether (Cook and Hewett, *J.*, 1936, 62), by the action of benzylmagnesium chloride on *cyclo*hexene oxide (Cook, Hewett, and Lawrence, *ibid.*, p. 75) and of sodium on a mixture of *cyclo*hexanol and benzyl alcohol (Guerbet reaction) (Weitzmann, Bergmann, and Haskelberg, *Chem. and Ind.*, 1937, 587), and by reaction of potassium benzyloxide with *cyclo*hexanone (Mastagli, Charreine, and Lambert, *Compt. rend.*, 1945, **221**, 749). The first of these methods might be expected, by analogy with the similar reduction of 2-methyl-*cyclo*hexanone (Skita, *Annalen*, 1923, **431**, 22) or that of other alkyl-substituted hydroaromatic ketones by sodium in ethanol (Vavon, *Bull. Soc. chim.*, 1926, **49**, 668, and later papers), to give the *trans*-isomer. The reaction of *cyclo*hexene oxide with Grignard reagents is usually complicated by rearrangements (Cook, Hewett, and Lawrence, *loc. cit.*;

Winstein and Henderson in Elderfield's " Heterocyclic Compounds," John Wiley and Sons, New York, Vol. I, 1950, p. 55). Benzylmagnesium chloride is remarkable in that it gives the normal product 2-benzyl*cyclo*hexanol (m. p. 77°) in about 50% yield (Cook *et al.*, *loc. cit.*). This is explained by these authors on the grounds that the dibenzylmagnesium, formed in the equilibrium $2PhCh_2MgCl \rightleftharpoons MgCl_2 + Mg(Ch_2Ph)_2$, is unusually reactive towards the oxide and leads to a preponderance of 2-benzyl*cyclo*hexanol in the product; since Bartlett and Berry (*J. Amer. Chem. Soc.*, 1934, **56**, 2683) have shown that the oxide and dialkylmagnesiums, or other nucleophilic reagents (Boeseken and van Giffen, *Rec. Trav. chim.*, 1920, **39**, 184), give almost exclusively *trans*-compounds, the product, isomer of m. p. 77°, should be the *trans*-form (II). Finally Weizmann *et al.* (*loc. cit.*) have shown that, in one case at least (2-butyl*cyclo*hexanol), the Guerbet reaction gives the *trans*-isomer exclusively.

In another connection, *cis*- and *trans*-2-benzyl*cyclo*hexanol were required. If the evidence for the *trans*-configuration of the product of m. p. 77° is correct then the Skita rule, either in the original form or as modified by Barton (*J.*, 1953, 1029, footnote 23), indicates that catalytic hydrogenation of 2-benzyl*cyclo*hexanone (III) in acidic medium should give the *cis*-alcohol. Catalytic reduction in acidified methanol with a platinum catalyst yielded only 2—3% of the known isomer: the bulk of the product did not crystallize. After several distillations the analysis of this compound and the derived 3 : 5-dinitrobenzoate (m. p. 129°) indicated a formula $C_{13}H_{18}O$. Since oxidation with chromic acid gave the ketone (III) there can be little doubt that this is the epimer, *cis*-2-benzyl*cyclo*hexanol (I).

2-Benzyl*cyclo*hexanone (III) has been prepared previously by Cook and Hewett (*loc. cit.*), Tiffeneau and Porcher (*Bull. Soc. chim.*, 1922, **31**, 331), and von Auwers and Treppmann (*Ber.*, 1915, **48**, 1222). In the present work it was prepared by catalytic



reduction of 2-benzylidene*cyclo*hexanone (IV) in methanol with a platinized charcoal catalyst (cf. Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 4586). After the absorption of one mol. of hydrogen the reduction ceased and pure 2-benzyl*cyclo*hexanone was isolated in *ca.* 80% yield. In acidic methanol in presence of platinum two mols. of hydrogen were absorbed, the second much the more slowly, to give mainly *cis*-2-benzyl*cyclo*hexanol (I) together with *ca.* 5% of the *trans*-compound.

The reduction of 2-benzyl*cyclo*hexanone (III) with lithium aluminium hydride gave almost pure *trans*-2-benzyl*cyclo*hexanol and is the method of choice for the preparation of this compound. 2-Benzylidene*cyclo*hexanone (IV) with this reagent gave 2-benzylidene-*cyclo*hexanol (V) in almost quantitative yield. The 1 : 2-reduction of αβ-unsaturated

ketones with the mixed hydride has been remarked previously (Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, New York, 1951, p. 469). The resemblance of the ultra-violet absorption spectrum of (V) ($\lambda_{max.}$ 2430 Å, ε 14,500) to that of styrene ($\lambda_{max.}$ 2440 Å, ε 12,000; see Braude in Rodd's "Chemistry of the Carbon Compounds," Elsevier, London, Vol. 1A, 1951, p. 71), together with the results of the catalytic reduction of the compound (see below), proves the structure.

2-Benzylidene*cyclo*hexanol (V) on catalytic hydrogenation with a platinized charcoal catalyst gave *cis*-2-benzyl*cyclo*hexanol (I) (*ca.* 50%) and a hydrocarbon $C_{13}H_{18}$ (*ca.* 45%); on conversion of the alcohols into the 3 : 5-dinitrobenzoates a very small amount of the *trans*-derivative was isolated. The reduction of (V) may be likened to that of cinnamyl alcohol with a palladized charcoal catalyst, which gives rise to 3-phenylpropanol and propylbenzene (Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984). In the present case the hydrocarbon $C_{13}H_{18}$ is almost certainly benzyl*cyclo*hexane (VI) but it was not rigidly identified. Hydrogenation of (V) in acidic medium with a platinum catalyst gave mainly (I) and some (II), but no hydrocarbon was detected.

Hydrogenation of 2-benzylidene*cyclo*hexanone in the presence of a little potassium carbonate with a platinum catalyst was slow. The products were 2-benzylidene*cyclo*hexanol (V) (*ca.* 60%), *cis*-2-benzyl*cyclo*hexanol (I) (*ca.* 30%), and a little *trans*-2-benzyl*cyclo*hexanol (II). Under the same conditions 2-benzyl*cyclo*hexanone (III) was not reduced and the catalyst was found to be partially poisoned when challenged with *cyclo*hexene. Accordingly it is believed that the unsaturated alcohol (V) is the main primary product in the reduction of unsaturated ketone (IV) under these conditions.

2-Benzyl*cyclo*hexanone was hydrogenated with difficulty in the presence of Raney nickel, the product being mainly the *cis*-alcohol (I).

The annexed reaction scheme shows only the main products.

Experimental

2-*Benzyl*cyclo*hexanone* (III).—2-Benzylidene*cyclo*hexanone (18·6 g.) (Wallach, *Ber.*, 1907, **40**, 71) in methanol (50 ml.) was shaken in hydrogen at *ca.* 30 lb. pressure with platinized charcoal (from 1 g. of charcoal and 0·1 g. of platinum, see Baltzly, *loc. cit.*). Uptake of hydrogen was rapid and reduction stopped after absorption of 1 mol. The catalyst was removed, the solvent evaporated off, the residue dissolved in ether, the ethereal solution stirred with a saturated solution of sodium hydrogen sulphite over-night, and the solid bisulphite compound collected and washed with ether. The bisulphite compound was dissolved in hot water (*ca.* 500 ml.), and the solution made acid with concentrated sulphuric acid. After cooling, the oily material was extracted with ether and washed with sodium hydrogen carbonate solution and with water. After being dried, the ether was removed and the ketone distilled (15 g.; b. p. 160°/12 mm.) (Cook and Hewett, *loc. cit.*, give b. p. 155/10 mm.). With semicarbazide hydrochloride in sodium acetate solution the semicarbazone, m. p. 168°, was formed [von Auwers and Treppmann, and Cook and Hewett (*locc. cit.*), give 166—167°].

The original solution after removal of any traces of ketone as the semicarbazone gave an oil which partly solidified on cooling (3 g.).

cis-2-*Benzyl*cyclo*hexanol* (I).—2-Benzyl*cyclo*hexanone (9 g.), in methanol (50 ml.) acidified with concentrated hydrochloric acid (0·5 ml.) was shaken with Adams's catalyst until uptake of hydrogen ceased. The catalyst and most of the methanol were removed, the solution was diluted with water, and the oil extracted with ether. The ethereal solution was washed with dilute sodium hydrogen carbonate solution and then with water. After being dried, the ether was removed and the residue was kept at 0° for 12 hr. after being seeded with the *trans*-alcohol. The very small amount of crystalline material (*ca.* 0·2 g.) was filtered off and the oily cis-*isomer* distilled (b. p. 90—95°/0·15 mm.; 7·5 g.) (Found: C, 82·5; H, 9·8. $C_{13}H_{18}O$ requires C, 82·2; H, 9·5%).

Treatment with 3 : 5-dinitrobenzoyl chloride in benzene–pyridine gave the 3 : 5-*dinitrobenzoate*, needles (from ether–hexane, methanol, or ethanol), m. p. 129° (Found: C, 62·6; H, 5·4. $C_{20}H_{20}O_6N_2$ requires C, 62·5; H, 5·2%).

trans-2-*Benzyl*cyclo*hexanol* (II).—2-Benzyl*cyclo*hexanone (9 g.) in ether (30 ml.) was added to a suspension of lithium aluminium hydride (2 g.) in ether (25 ml.) during 2 hr., with stirring. The mixture was then refluxed for 4 hr. and, after cooling, the reagent was decomposed by the addition of water. The ethereal layer, after being washed with water and dried, gave on

evaporation an oil which solidified (8·0 g.). Recrystallization from pentane gave needles, m. p. 77°. The 3 : 5-dinitrobenzoate formed prisms, m. p. 134°, from ethanol. These were contaminated with very small quantities of the *cis*-ester from which they were separated by virtue of their lower solubility. Both the alcohol, m. p. 77°, and the 3 : 5-dinitrobenzoate, m. p. 134°, were identical with samples prepared by the reduction of 2-benzyl*cyclo*hexanone with sodium in moist ether (Cook and Hewett, *loc. cit.*).

Oxidation of cis- *and* trans-2-*Benzyl*cyclo*hexanols with Chromic Acid.*—The *cis*- or the *trans*-alcohol with cold chromic acid (cf. Cook, Hewett, and Lawrence, *loc. cit.*) gave 2-benzyl*cyclo*hexanone, the semicarbazone of which melted at 168° alone or mixed with the sample previously described.

trans-2-*Benzyl*cyclo*hexyl Toluene*-p-*sulphonate.*—The alcohol (5 g.) and toluene-*p*-sulphonyl chloride (7 g.) were kept in pyridine (25 ml.) at room temperature for 48 hr. Recovery as usual and several crystallizations from ether–ligroin gave the *ester* as needles, m. p. 94—95° (Found : C, 69·9; H, 7·0. $C_{20}H_{24}O_3S$ requires C, 69·7; H, 7·0%).

Reduction of 2-*Benzylidene*cyclo*hexanone with Platinum in Acid Solution.*—The unsaturated ketone (9·3 g.) in methanol (50 ml.) containing methanolic hydrogen chloride (0·5 ml. of 40%) was shaken with hydrogen and Adams's catalyst. The first mol. of hydrogen was absorbed rapidly but the second at only one-twelfth of the original rate. The product was worked up as in the first example above. In all 9 g. of distilled *cis*-benzyl*cyclo*hexanol were obtained (b. p. 90—93°/0·15 mm.). The 3 : 5-dinitrobenzoate prepared from this alcohol appeared to be pure *cis*-compound, m. p. 129° after recrystallization from ethanol.

2-*Benzylidene*cyclo*hexanol* (V).—2-Benzylidene*cyclo*hexanone (9 g.) in ether (25 ml.) was added to a suspension of powdered lithium aluminium hydride (4 g.) in ether (50 ml.) with stirring during *ca.* 1 hr. Stirring was continued and the mixture refluxed for 2 hr. Decomposition with water, washing with water, drying, and removal of the ether gave an oil which crystallized (8·7 g.). Recrystallization from pentane gave 2-*benzylidene*cyclo*hexanol* as needles, m. p. 63—64° (Found : C, 83·1; H, 8·6. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%). Ultra-violet max. at 243 mμ (ε 14,500 in EtOH) (Beckman model DU quartz spectrophotometer; cell length 1 cm.).

Catalytic Reduction of 2-*Benzylidene*cyclo*hexanol.*—The unsaturated alcohol (5 g.) in methanol was shaken with platinized charcoal in hydrogen at about 30 lb. pressure, 1 mol. being absorbed in 11 hr. before the reduction stopped. The catalyst was removed, the methanol evaporated off, and the residue dissolved in ether and washed with water. The ethereal solution, after being dried, was evaporated, to give an oil (*ca.* 4·5 g.). On acylation with 3 : 5-dinitrobenzoyl chloride in pyridine the main product was the ester, m. p. 129° (5·0 g.), of *cis*-2-benzyl*cyclo*hexanol, together with 0·1 g. of the *trans*-ester. Some oil which had resisted acylation was also obtained, probably *benzyl*cyclo*hexane* (b. p. 40—45°/0·2 mm.; 1·7 g.) (Found : C, 89·8; H, 10·5. $C_{13}H_{18}$ requires C, 89·7; H, 10·3%).

Catalytic Reduction of 2-*Benzylidene*cyclo*hexanone in Methanol containing Potassium Carbonate.*—The unsaturated ketone (IV) (5 g.) and potassium carbonate (100 mg.) and Adams catalyst were hydrogenated in methanol (50 ml.). One mol. was absorbed at a moderate rate and the second much more slowly, total absorption being about 1·5 mols. The product consisted of about 60—70% of 2-benzylidene*cyclo*hexanol (V) which had its correct m. p. (64°) only after several recrystallizations from pentane; this was identified by m. p., mixed m. p., and ultra-violet spectrum. The residues were converted into the 3 : 5-dinitrobenzoates, the ester, m. p. 129° (2·5 g.), of the *cis*-, and that, m. p. 133—135° (0·2—0·3 g.), of the *trans*-alcohol being isolated by crystallization from methanol.

Raney Nickel Reduction of 2-*Benzyl*cyclo*hexanone.*—The ketone (5 g.), potassium carbonate (100 mg.), and Raney nickel (*ca.* 2 g.) in methanol (50 ml.) were hydrogenated. Uptake was slow and the reaction was stopped after about 0·67 mol. had been absorbed. The catalyst was removed and the methanol solution evaporated to give an oil. After removal of any unreduced ketone by sodium hydrogen sulphite the residual oil was converted into the 3 : 5-dinitrobenzoate, which on crystallization proved to be mainly the *cis*-ester, m. p. 129° (4 g.).

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The Halogenation of Phenolic Ethers and Anilides. Part XVI. Kinetics of the Chlorination of Diphenylyl and Naphthyl Ethers.*

By Brynmor Jones and J. P. Sleight.

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Extensive investigations (Parts I—XIV, *J.*, 1928—1943) of the rates of nuclear chlorination of aromatic ethers have shown that substituents exert their effects on reaction rates mainly, if not entirely, through changes in the energy of activation, without markedly affecting the probability factor P of the modified Arrhenius equation, $k = PZe^{-E/RT}$. For the ethers p-RO·C_6H_4·X especially the results accord with the view that the substituents OR and X contribute additively to the value of E. A similar analysis of velocity coefficients has now been made for series of diphenylyl ethers and for some naphthyl ethers.

In the diphenylyl series the results, taken as a whole, conform closely with those found among the phenyl ethers, although the ratios of the velocity coefficients for the ethers RO·C_6H_4·C_6H_4·X show slight variations from the values found in the earlier series.

In the naphthyl series, on the other hand, some divergences were observed.

The quantitative study of the nuclear chlorination of aromatic ethers has been extended to include several series of ethers derived from 4-hydroxydiphenyl and from 1-naphthol. As in the simpler phenolic ethers, deactivating substituents, such as the halogens and the nitro-group, were introduced in order to bring the rates within the range of accurate measurement, and to confine substitution to a single nuclear position. In the diphenylyl series, most of the ethers carried a deactivating substituent in the second ring, and were mostly of the type RO·C_6H_4·C_6H_4·X. In the naphthol series, ethers of 2- and 4-nitro- and 2- and 4-chloro-1-naphthol have been studied.

Table 1. *Diphenylyl Ethers. Velocity coefficients for the chlorination of ethers of the types :* (*a*) RO·C_6H_4·C_6H_4X, (*b*) 4 : 3-RO·C_6H_3Cl·C_6H_4·NO_2-4, *and* (*c*) [4 : 3-RO·C_6H_3Cl·]$_2$ *in* 99% *acetic acid*, at 20°.

$[Cl_2] = 0{\cdot}005$; [ether] = 0·010; [HCl] = 0·025.

	Type X	R = Me	Et	Pr^n	Pr^i	Bu^n
(*a*)	4-Nitro	8·27	15·66	16·97	32·9	—
	4-Fluoro	47·4	91·8	—	—	—
	4-Chloro	36·7	71·0	—	148	—
	4-Bromo	34·2	65·4	—	—	—
	H	76	144	163	293 *	162
	2-Nitro	22·3	43·1	47·9	93·1	—
(*b*)		0·019	0·0387	0·0415	0·0564	—
(*c*)		0·362	0·716	0·771	0·977	—

$[Cl_2] = 0{\cdot}0025$; [ether] = 0·005; [HCl] = 0·0125.

	Ether	R = Me	CH_2Ph	p-NO_2·C_6H_4·CH_2·
(*a*)	X = 4-Nitro	7·91	5·35	—
	H	74·7	54·3	10·37

* This represents a very rapid reaction which is complete within a few minutes.

The velocity coefficients are recorded in Tables 1 and 3 and the velocity ratios in Tables 2 and 4. The method of determining the rates was the same as in previous investigations, and the values were calculated from the usual expression for a bimolecular reaction, the unit of time being the minute and of concentration mole l.$^{-1}$. The relative directive powers of alkoxy-groups are expressed in the usual form 100 k_X^{OR}/k_X^{OMe}.

Diphenylyl Ethers.—Table 2, where the relative directive effects of alkoxy-groups are summarised, shows that for several series of diphenylyl ethers the values of the relative directive effects of these groups agree closely with those found for the simpler ethers,

* Part XV, *J.*, 1949, 1389.

$RO{\cdot}C_6H_4X$. The measure of this agreement is best seen from Table 6, which gives the mean values for the several series of diphenylyl and phenyl ethers.

TABLE 2. *Relative directive effects of the groups* OR *in compounds of the above types. Values of* $100k_X^{OR}/k_X^{OMe}$.

Type X	R = Me	Et	Pr^n	Pr^i	Bu^n	CH_2Ph	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
(*a*) 4-Nitro	100	190	205	398	—	68	—
4-Fluoro	100	194	—	—	—	—	—
4-Chloro	100	193	—	402	—	—	—
4-Bromo	100	191	—	—	—	—	—
H	100	190	215	385	213	73	13·9
2-Nitro	100	194	215	417	—	—	—
(*b*)	100	204	218	297	—	—	—
(*c*)	100	198	213	270	—	—	—
Phenyl ethers (mean)	100	199	223	440	223	68	14·1

TABLE 3. *Naphthyl ethers. Velocity coefficients for the chlorination of ethers of the types* (a) 1 : 2-$RO{\cdot}C_{10}H_6{\cdot}X$ *and* (b) 1 : 4-$RO{\cdot}C_{10}H_6{\cdot}X$ *in* 99% *acetic acid, at* 20°.

$[Cl_2] = 0{\cdot}005$; [ether] = 0·010; [HCl] = 0·025.

Type X	R = Me	Et	Pr^n	CH_2Ph	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
(*a*) NO_2	0·728	1·005	—	—	0·097
Cl	14·64	22·87	27·06	10·75	2·40
(*b*) NO_2	42·5	75·2	72·0	25·2	—

$[Cl_2] = 0{\cdot}001$; [ether] = 0·002; [HCl] = 0·005.

Type of ether	R = Me	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
(*b*) NO_2	39·5	6·38
Cl	—	*ca.* 650

TABLE 4. *Relative directive effects of the groups* OR *in compounds of the above types. Values of* $100k_X^{OR}/k_X^{OMe}$.

Type X	R = Me	Et	Pr^n	CH_2Ph	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
(*a*) NO_2	100	139	—	—	13·3
Cl	100	156	184	73	16·4
(*b*) NO_2	100	177	170	59	16·2

TABLE 5. *Phenyl ethers. Velocity coefficients for the chlorination of ethers of o-nitrophenol in* 99% *acetic acid, at* 20°.

$[Cl_2] = 0{\cdot}005$; [ether] = 0·05; [HCl] = 0·025.

R = Me	Et	Pr^n
0·0180	0·0362	0·0414

Relative directive effects of the groups OR *in ethers of* o-*nitrophenol. Values of* $100k_X^{OR}/k_X^{OMe}$.

	R = Me	Et	Pr^n
	100	203	230
Phenyl ethers (mean)	100	199	223

TABLE 6. *Mean relative directive powers of alkoxy-groups. Values of* $100k_X^{OR}/k_X^{OMe}$.

	R = Me	Et	Pr^n	Pr^i	Bu^n	$PhCH_2$	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
Diphenylyl ethers	100	194	213	361 *	213	70	13·9
Phenyl ethers	100	199	223	440	223	68	14·1

* The value for the *iso*propoxy-group in the diphenylyl series must not be regarded as strictly comparable since it includes values for ethers which have a polar substituent adjacent to the *iso*-propoxy-group. It has been previously shown that this gives rise to anomalous results in the phenyl ethers.

In accordance with previous results, such agreement indicates that in the diphenylyl ethers the probability factor of the modified Arrhenius equation is essentially constant. This was confirmed by an analysis of the velocity coefficients for a number of diphenylyl ethers at 20° and 35°. In a plot of the energies of activation against the values of $3 \log_{10} k_{20}$ all the points fall on or near to the line of slope $-2{\cdot}303\boldsymbol{R}T$ given in Part XII

(*J.*, 1942, 418). Because many of the ethers are highly reactive, only a limited number could be investigated in this way, but among those examined the values of E and of $\log PZ$ respectively ranged from 13,170 cals. and 8·44 for 3-chloro-4-ethoxy-4′-nitrodiphenyl to 10,170 cals. and 8·52 for 4-methoxy-4′-nitrodiphenyl.

It is interesting to speculate to what extent a series of diphenylyl ethers, p-RO·C_6H_4·C_6H_4X, may be compared with the simpler phenyl ethers, p-RO·C_6H_4X, for, despite the obvious similarity in the directive powers of alkoxy-groups, there are small differences. If the bond uniting the two nuclei in the diphenylyl ethers is an invariable single bond, the group C_6H_4X may be regarded as a single substituent, in which case the relative effects of the alkoxy-groups would be expected to be the same as in the phenyl series. On the other hand, if, as is generally believed, this bond possesses some double-bond character interaction between the two benzene rings, with the consequent distribution of electronic charges over two instead of one nucleus, may occur to a degree varying with the polar character of the substituent (Le Fèvre and Le Fèvre, *J.*, 1936, 1130; Lennard-Jones and Turkevitch, *Proc. Roy. Soc.*, 1937, *A*, **158**, 297; Dhar, *Proc. Nat. Inst. Sci. India*, 1949, **15**, 11; *Chem. Abs.*, 1949, **43**, 4655). Such effect may account for the small differences in the diphenylyl and phenyl ethers, but differences of this order (cf. Table 6) may also be expected from the experimental errors.

Apart from their bearing on the effect which substituents exert on the energy of activation, and on the additive nature of these effects, our results afford a comparison between the deactivating effect of substituents in ethers of the two types p-RO·C_6H_4·C_6H_4X and p-RO·C_6H_4X. As expected, the deactivating influence of X is very much greater when it is situated in the nucleus undergoing chlorination. The magnitude of this difference is significant, for, whereas the rate of chlorination of anisole is of the order 1×10^3, and that of p-nitroanisole is $2{\cdot}9 \times 10^{-3}$, the velocity coefficients for 4-methoxydiphenyl and 4-methoxy-4′-nitrodiphenyl are 76 and 8·3, respectively. The following velocity coefficients illustrate this effect in greater detail for three of the halogens and for the nitro-group.

Velocity coefficients at 20°.

Ether	X = H	F	Cl	Br	NO_2
p-MeO·C_6H_4X	—	2·35 *	1·23	1·26	0·0029
4-MeO·C_6H_4·C_6H_4X-4	76·0	47·4	36·7	34·2	8·3
4-MeO·C_6H_4·CO·C_6H_4X-4	1·26	1·07	0·87	0·85	0·385

* Calculated from the observed value for the benzyl ether, cf. *Trans. Faraday Soc.*, 1941, **37**, 739.

These results are as expected, but the magnitude of the effects is here brought out clearly for the first time. A nitro-group in a diphenylyl ether reduces the rate of chlorination of the parent ether 9-fold, whereas in the phenyl series, the reduction is of the order of 10^6.

The values for the diphenylyl ethers may also be compared with those for ethers based on benzophenone (cf. Part VIII) in which the carbonyl group interpolated between the two benzene rings imposes an electronic constraint and so suppresses further the effect of a polar substituent. So powerful a polar substituent as a nitro-group only reduces three-fold the rate of chlorination of 4-methoxybenzophenone.

Naphthyl Ethers.—An extensive study of naphthyl ethers has not been possible because of their high reactivity and the consequent difficulties in obtaining accurate measurements, and Table 3 shows the range of compounds examined to be restricted to ethers derived from 2- and 4-nitro-1-naphthol and from 2- and 4-chloro-1-naphthol.

Although limited in scope, the results (Table 4) show that, taken as a whole, the relative directive effects of OR groups in naphthalene compounds differ appreciably from the values found for phenyl and diphenylyl ethers. The influence of the various alkoxy-groups on the rates of chlorination remain in the order EtO > MeO > $PhCH_2$·O > p-NO_2·C_6H_4·CH_2·O, but their relative directive effects are less widely spaced. Moreover, these effects do appear here to be dependent on the nature of the second substituent.

These results are only a first study in the naphthalene series. A more comprehensive investigation is necessary before the results can be compared satisfactorily with those in the simpler aromatic ethers. They do, however, illustrate a number of points. First,

they confirm the higher general reactivity of naphthalene compounds as compared with benzene compounds, as is borne out by the following rate constants:

	Substituent			
	4-NO_2	4-Cl	2-NO_2	2-Cl
Substituted 1-naphthyl methyl ethers	42·5	*ca.* 4 × 10^3	0·728	14·6
Substituted anisoles	0·0029	1·26	0·018	4·44

Secondly, they show that, whereas in the benzene series the *ortho*-substituted ether is more reactive than the corresponding *para*-substituted compound (cf. Table 5 and *J.*, 1935, 1831, 1835), in the naphthalene series the 2-substituted ether is far less reactive than its 4-substituted isomer (cf. Table 3).

Experimental

Purification of Acetic Acid.—Orton and Bradfield's method (*J.*, 1927, 983), whereby commercial acetic acid is distilled from "AnalaR" chromium trioxide and the calculated amount of pure acetic anhydride, unexpectedly failed with some post-war materials to give a satisfactory medium, and it was eventually found that the "purified" acetic acid contained a small amount of hydrochloric acid, which, by reacting with the dichloramine-T used in the velocity measurements, liberated enough free chlorine to start the reaction prematurely. The "purified" acetic acid was therefore re-distilled from solid silver acetate. In addition the method used earlier for determining the rate constants was modified by reducing the length of time the aromatic ether and the dichloramine-*T* were together in solution before the reaction was started. Any risk that the reaction might be started by a trace of hydrochloric acid was thereby removed.

Determination of Rate Constants.—The following procedure was adopted. The aromatic ether was dissolved in acetic acid (80—85 ml.) in a 100-ml. standard flask, and water ($1 - x$) ml., where x ml. is the amount of water in 100 ml. of the acid plus the water added in the constant-boiling hydrochloric acid, was added. The flask was then maintained at 20° for 30 min. After the requisite amount of dichloramine-T solution at 20° had been added, acetic acid, also at 20°, was added to bring the total volume to within y ml. of the graduation mark; y ml. of constant-boiling hydrochloric acid (being the calculated amount) were quickly added and the flask was shaken thoroughly and replaced in the thermostat. A stop-watch was started simultaneously with the first shake of the flask, and 10 ml. portions were withdrawn at intervals for estimation of the free chlorine. With these precautions, constant and reproducible results were always obtained.

To ensure the purity of the ethers, solid ethers were crystallised at least three times, usually from methanol, ethanol, or acetic acid, and liquid ethers were fractionally distilled until a constant value was obtained for the velocity coefficient, which was found to be a more reliable criterion of purity than the usual physical constants. The following random selection of examples illustrates the constancy of the mean values in individual experiments: (*a*) 4′-nitro-4-*iso*propoxydiphenyl had $k = 32·9$ after two crystallisations from methyl alcohol and one from acetic acid, and $k = 33·0$ and 32·9 after two further crystallisations from methyl alcohol; (*b*) 2-chloro-1-naphthyl ethyl ether, a liquid, had $k = 22·9$ and 23·1 after three fractional distillations, and $k = 22·5$ and 23·0 after two later distillations.

Unless otherwise stated, the ethers were prepared by standard methods from the phenol and the appropriate alkyl, aryl, or substituted aryl bromide or iodide. Methyl ethers were usually prepared by the action of methyl sulphate on an aqueous solution of the sodium phenoxide.

(a) *Diphenylyl ethers.* 4-Hydroxy-4′- and -2′-nitrodiphenyls were prepared by Brynmor Jones and Chapman's method (*J.*, 1952, 1829). From 4-hydroxy-4′-nitrodiphenyl the following 4′-nitro-4-diphenylyl ethers were prepared: methyl, m. p. 110°; *ethyl*, yellow prisms (from methyl alcohol), m. p. 107—108° (Found: C, 69·3; H, 5·5. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4%); n-*propyl* and iso*propyl*, pale yellow plates (from methyl alcohol), m. p. 74—75° (Found: C, 69·5; H, 6·1. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9%) and m. p. 77—78° (Found: C, 70·1; H, 5·8%), respectively; *benzyl*, yellow plates (from glacial acetic acid), m. p. 171—172° (Found: C, 74·7; H, 4·8. $C_{19}H_{15}O_3N$ requires C, 74·7; H, 4·9%); 2:4-*dinitrophenyl*, a microcrystalline powder (from a large volume of alcohol), m. p. 168° (Found: C, 56·4; H, 2·8. $C_{18}H_{11}O_7N_3$ requires C, 56·7; H, 2·9%).

From 4-hydroxy-2′-nitrodiphenyl the following 2′-nitro-4-diphenylyl ethers were obtained: *methyl*, *ethyl*, and iso*propyl*, yellow slender prisms (from methyl alcohol), m. p. 61—62° (Found:

C, 68·2; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%), m. p. 54—55° (Found: C, 69·1; H, 5·3. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4%), and m. p. 43—44° (Found: C, 70·8; H, 5·9. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9%), respectively; n-*propyl* ether, a yellow liquid, b. p. 180°/5 mm. (Found: C, 70·7; H, 6·2%).

4-Chloro-4′-hydroxydiphenyl was prepared by chlorinating 4-diphenylyl acetate in carbon tetrachloride containing a trace of iodine as catalyst, and hydrolysing the resulting chlorodiphenylyl acetates with alcoholic hydrogen chloride (cf. Savoy, *Proc. Louisiana Acad. Sci.*, 1947, **10**, 205; *Chem. Abs.*, 1948, **42**, 1919). After four crystallisations from aqueous acetic acid 4-chloro-4′-hydroxydiphenyl was obtained as a crystalline solid, m. p. 147—148°, and from this three 4′-chloro-4-diphenylyl ethers were prepared: *methyl*, m. p. 105° (Found: C, 71·0; H, 5·3. $C_{13}H_{11}OCl$ requires C, 71·4; H, 5·1%); *ethyl*, m. p. 123° (Found: C, 72·4; H, 5·3. $C_{14}H_{13}OCl$ requires C, 72·3; H, 5·6%); both crystallised from aqueous ethanol in clusters of plates, while the *isopropyl ether* separated from the same solvent as plates, m. p. 127—128° (Found: C, 73·2; H, 6·2. $C_{15}H_{15}OCl$ requires C, 73·0; H, 6·1%).

4-Bromo-4′-hydroxydiphenyl was obtained as follows: 4-nitrodiphenyl (Bell, Kenyon, and Robinson, *J.*, 1926, 1242) was brominated by Le Fèvre and Turner's method (*J.*, 1926, 2045) and the 4′-nitro-compound reduced by stannous chloride and concentrated hydrochloric acid (Bell and Robinson, *J.*, 1927, 1127). Diazotisation of the 4-amino-compound, followed by decomposition of the diazonium salt with dilute sulphuric acid, gave the 4-bromo-4′-hydroxydiphenyl as a solid, m. p. 165—167°, after crystallisation from alcohol (cf. Gray, Hartley, and Brynmor Jones, *J.*, 1952, 1959, for an improved synthesis of this compound). The *methyl* and *ethyl ethers* crystallised from aqueous acetic acid in silky plates, m. p. 145° (Found: C, 59·0; H, 4·4. $C_{13}H_{11}OBr$ requires C, 59·3; H, 4·2%) and m. p. 139° (Found: C, 60·4; H, 4·9. $C_{14}H_{13}OBr$ requires C, 60·7; H, 4·7%), respectively.

4-*Fluoro*-4′-*methoxydiphenyl*, which crystallised from ethyl alcohol as slender prisms, m. p. 90—91° (Found: C, 77·1; H, 5·6. $C_{13}H_{11}OF$ requires C, 77·2; H, 5·5%), was prepared as follows. 4-Methoxy-4′-nitrodiphenyl was reduced to the amino-compound by West's method (*J.*, 1925, **127**, 494). When the amino-compound had been diazotised, 4-methoxydiphenyl-4′-diazonium borofluoride was precipitated by the addition of an excess of sodium borofluoride solution to the cold diazonium solution. The carefully dried diazonium fluoroborate was then decomposed by heat to the methyl ether (cf. Balz and Schiemann, *Ber.*, 1927, **60**, 1186). 4-*Ethoxy*-4′-*fluorodiphenyl*, prepared similarly, crystallised from ethyl alcohol in small plates, m. p. 99° (Found: C, 77·8; H, 5·9. $C_{14}H_{13}OF$ requires C, 77·8; H, 6·1%).

From 4-hydroxydiphenyl seven diphenylyl ethers were prepared. The methyl, ethyl, *n*- and *iso*propyl, and *n*-butyl ethers had m. p.s 88—89°, 76°, 76°, 73°, and 75°, respectively (cf. Brewster and Puttman, *J. Amer. Chem. Soc.*, 1939, 3083). The *benzyl ether* crystallised from acetic acid in plates, m. p. 129° (Found: C, 87·6; H, 6·2. $C_{19}H_{16}O$ requires C, 87·7; H, 6·2%), and the p-*nitrobenzyl ether*, m. p. 164—165° (Found: C, 75·0; H, 4·8. $C_{19}H_{15}O_3N$ requires C, 74·8; H, 4·9%), separated from acetic acid–ethyl alcohol in pale yellow plates.

3-Chloro-4′-nitro-4-diphenylyl ethers were obtained by the chlorination of 4-alkoxy-4′-nitrodiphenyls in acetic acid, the chlorine being generated from the calculated amount of dichloramine-T with concentrated hydrochloric acid. The *methyl ether* crystallised from acetic acid and from acetic acid–ethyl alcohol as clusters of pale yellow prisms, m. p. 143—144° (Found: C, 59·0; H, 3·7. $C_{13}H_{10}O_3NCl$ requires C, 59·2; H, 3·8%). The *ethyl*, n-*propyl*, and iso-*propyl ethers*, obtained as yellow prisms from methyl alcohol, had m. p. 106—107° (Found: C, 60·4; H, 4·5. $C_{14}H_{12}O_3NCl$ requires C, 60·5; H, 4·4%), m. p. 64—65° (Found: C, 62·0; H, 4·6. $C_{15}H_{14}O_3NCl$ requires C, 61·8; H, 4·8%), and m. p. 68—69° (Found: C, 61·6; H, 4·9%), respectively.

3 : 3′-Dichloro-4 : 4′-dihydroxydiphenyl was prepared by the chlorination of 4 : 4′-dihydroxydiphenyl in acetic acid solution with dichloramine-T and hydrochloric acid. It crystallised from a large volume of water as small prisms, m. p. 128°. Its *dimethyl ether* crystallised from ethyl alcohol and from acetic acid in plates, m. p. 157—158° (Found: C, 59·0; H, 4·2. $C_{14}H_{12}O_2Cl_2$ requires C, 59·4; H, 4·3%). The *diethyl* and *diisopropyl ethers* separated from ethyl and methyl alcohols as plates, m. p. 116—117° (Found: C, 61·3; H, 5·1. $C_{16}H_{16}O_2Cl_2$ requires C, 61·7; H, 5·2%), and m. p. 80° (Found: C, 63·3; H, 6·0. $C_{18}H_{20}O_2Cl_2$ requires C, 63·7; H, 5·9%), respectively. The *di*-n-*propyl ether* was obtained from methyl alcohol as prisms, m. p. 65—66° (Found: C, 63·3; H, 5·9. $C_{18}H_{20}O_2Cl_2$ requires C, 63·7; H, 5·9%).

(b) *Naphthyl ethers.* 4-Nitro-1-naphthol, m. p. 164°, was obtained by the alkaline hydrolysis of 4-nitro-1-naphthylamine, prepared by Hodgson and Walker's method (*J.*, 1933, 1205). Its

methyl ether, prepared by Hodgson and Smith's method (*J.*, 1935, 672), crystallised from alcohol in yellow-orange prisms, m. p. 82—83°. Woroshzoff (*Zeitsch. Farb. Ind.*, 1911, **10**, 169) gave m. p. 81°; Hodgson and Smith, 85°. The ethyl ether also separated from alcohol as yellow prisms, m. p. 115°, while the n-*propyl ether* crystallised from ethyl and methyl alcohols as yellowish-brown prisms, m. p. 66° (Found: C, 67·2; H, 5·7. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7%). The *benzyl* and p-*nitrobenzyl ethers* had m. p. 91—92° (Found: C, 72·9; H, 4·6. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·7%), and m. p. 189° (Found: 63·3; H, 3·8. $C_{17}H_{12}O_5N_2$ requires C, 63·0; H, 3·7%), respectively.

2-Nitro-1-naphthol was obtained by Hodgson and Kilner's method (*J.*, 1924, 807); it crystallised from alcohol in slender orange-yellow prisms, m. p. 128°. The methyl ether was prepared by treating dry sodium 2-nitro-1-naphthoxide with methyl sulphate and xylene for 3 hr. at 145°. After unchanged sulphate had been hydrolysed with hot aqueous sodium hydroxide, the cooled mixture was extracted with ether and dried. Evaporation of the ether, followed by addition of a small amount of light petroleum (b. p. 60—80°) precipitated the methyl 2-nitro-1-naphthyl ether. Three crystallisations from light petroleum gave yellow prisms, m. p. 80—81° (Clemo, Cockburn, and Spence, *J.*, 1931, 1271, gave m. p. 80°). The *ethyl ether*, similarly prepared, was obtained by steam-distillation as a yellow liquid. After purification by fractional distillation, it crystallised from light petroleum (b. p. 40—60°) as fine yellow prisms, m. p. 25—26° (Found: C, 66·1; H, 5·2. $C_{12}H_{11}O_3N$ requires C, 66·3; H, 5·1%). Heermann (*J. pr. Chem.*, 1891, **44**, 240) reported this ether as yellow needles, m. p. 84°. Attempts to prepare ethyl 2-nitro-1-naphthyl ether by Heermann's method resulted in the isolation of the 4-nitro-isomer, m. p. 115°. The p-*nitrobenzyl* 2-*nitro*-1-*naphthyl ether* crystallised from aqueous acetic acid–methyl alcohol and from acetic acid as slender yellow prisms, m. p. 141—142° (Found: C, 63·1; H, 3·9. $C_{17}H_{12}O_5N_2$ requires C, 63·0; H, 3·7%).

4-Chloro-1-naphthol, prepared by treating a solution of α-naphthol in chloroform with sulphuryl chloride (Lesser and Gad, *Ber.*, 1923, **56**, 972), and purified by crystallisation from chloroform, had m. p. 120—121°. The *benzyl* and 2 : 4-*dinitrophenyl ethers* separated from aqueous acetic acid as prisms, m. p. 94° (Found: C, 75·5; H, 4·8. $C_{17}H_{11}OCl$ requires C, 76·0; H, 4·9%), and as yellow prisms, m. p. 130° (Found: C, 55·7; H, 2·5. $C_{16}H_9O_5N_2Cl$ requires C, 55·7; H, 2·6%), respectively. The p-*nitrobenzyl ether* crystallised from acetic acid and had m. p. 145° (Found: C, 64·9; H, 3·9. $C_{17}H_{12}O_3NCl$ requires C, 65·1; H, 3·9%).

4-Chloro-1-naphthyloxyacetic acid after several crystallisations from aqueous acetic acid melted at 167° (Haskelberg, *J. Org. Chem.*, 1947, **12**, 426, gave m. p. 169°). Steam-distillation of the mother-liquors obtained in the preparation of 4-chloro-1-naphthol gave 2-chloro-1-naphthol as an impure greyish-white solid (cf. Lesser and Gad, *loc. cit.*). Crystallisation from light petroleum (b. p. 40—60°) failed to purify it—the best specimen melted 2—3° lower than the pure product, and ethers prepared from such specimens gave unsatisfactory velocity coefficients. The 2-chloro-1-naphthol was eventually purified by conversion into its toluene-*p*-sulphonyl ester (pyridine being used as solvent), and this was readily purified by crystallisation from methyl alcohol and from acetic acid. Hydrolysis of the pure ester, m. p. 101°, gave a specimen of the 2-chloro-1-naphthol which, after one crystallisation from light petroleum (b. p. 40—60°), melted sharply at 64—65°. The *methyl ether* crystallised from methyl alcohol as prisms, m. p. 42—43° (Found: C, 68·7; H, 4·7. $C_{11}H_9OCl$ requires C, 68·6; H, 4·7%). The p-*nitrobenzyl ether* crystallised from ethyl alcohol in clusters of prisms, m. p. 101—102° (Found: C, 64·8; H, 4·1. $C_{17}H_{12}O_3NCl$ requires C, 65·1; H, 3·9%). The *ethyl* and n-*propyl ethers* were liquids, b. p. 130°/4 mm. (Found: C, 70·0; H, 5·7. $C_{12}H_{11}OCl$ requires C, 69·7; H, 5·4%) and b. p. 140°/3 mm. (Found: C, 71·1; H, 6·7. $C_{13}H_{13}OCl$ requires C, 70·7; H, 5·9%), respectively. The *benzyl ether* was obtained as a brownish liquid, which, after fractional distillation, crystallised from methyl alcohol in clusters of prisms, m. p. 49—50° (Found: C, 76·1; H, 5·1. $C_{17}H_{13}OCl$ requires C, 76·0; H, 4·9%).

(c) *Phenyl ethers.* *o*-Nitroanisole and *o*-nitrophenetole were obtained as yellow liquids, b. p. 142°/12 mm. and 148°/21 mm., respectively, from *o*-nitrophenol. *o*-Nitrophenyl *n*-propyl ether was prepared by an adaptation of Richardson's method (*J.*, 1926, 522) from *o*-chloronitrobenzene and *n*-propyl alcohol and had b. p. 157—158°/17 mm.

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Temperature and the Optical Rotatory Power of Solutions. 9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene.*

By M. K. Hargreaves.

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The specific rotatory powers of solutions of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene do not decrease with rise of temperature but appear to rise slightly.

It was recently shown (Hargreaves, *J.*, 1953, 2953) that the rotatory power of octan-2-ol in *n*-heptane varies little, if at all, with change of temperature in the region 25—60°, the slight general rise with increase of temperature being of the order of the probable error of the measurements. The effect of temperature on the rotatory power of solutions of simple organic solutes has hardly been investigated at all, most of the available data referring to homogeneous active liquids in which a reduction of rotatory power usually, though not invariably, obtains (Pickard and Kenyon, *J.*, 1912, **101**, 1427; 1913, **103**, 1933; Kenyon, *J.*, 1914, **105**, 2247; Hargreaves, *loc. cit.*). Rule and Chambers (*J.*, 1937, 149) found that the rotatory power of (+)-pinane is reduced with rising temperature when in solution in nitrobenzene or mesitylene, whilst with (+)-pinene the rotatory power decreases in the first solvent and increases in the second. Rule attributed this difference of behaviour to the polarity of the solute. Rule, Barnett, and Cunningham (*J.*, 1933, 1222) have related the effect of solvent on the rotatory power of the solute to the refractive indices of the solvents.

Through the kindness of Dr. D. Muriel Hall it has been possible to examine, with this point in view, the rotatory dispersion in the visible region of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene in dilute solution. This substance is particularly suitable since it has a very high rotatory power, is a hydrocarbon, and presumably has only one configuration. Its chief disadvantage is its low solubility—the solutions employed had a concentration of about 0·2%.

Table 1. *Specific rotatory powers of solutions of* 9 : 10-*dihydro*-3 : 4-5 : 6-*dibenzophenanthrene.*

The rotatory powers have been corrected for the change in the number of active molecules in the light path with temperature (by density corrections) and also for the evaporation of the solvent. In the series (*a*) the correction has been for half the gain in activity of the solution due to evaporation; in series (*b*) it has been corrected for the full amount.

Solvent					Wave-length, Å								
				C								$[\alpha]_{4358}$	$[\alpha]^{(b)}_{4358}$
(l = 2)	t		d	(g./100 c.c.)	6438	5780	5461	5086	4800	4678	4358	$[\alpha]_{5461}$	$[\alpha]^{(a)}_{5461}$
CCl_4	25°		1·5843	0·2297	847°	1099°	1265°	1502°	1720°	1824°	2099°	1·659	
	40	(*a*)	1·5550	0·2254	—	1121	1282	—	—	—	2176	1·697	1·689
		(*b*)	—	—	—	1115	1276	—	—	—	2165	1·697	
	51	(*a*)	1·5333	0·2223	—	—	1300	—	—	—	2198	1·691	1·688
		(*b*)	—	—	—	—	1298	—	—	—	2194	1·690	
Benzene	25		0·87341	0·1620	935	1309	1494	1812	2068	2173	2528	1·692	—
	37	(*a*)	0·86053	0·1596	—	1313	1503	—	—	—	2549	1·696	1·689
		(*b*)	—	—	—	1308	1497	—	—	—	2538	1·695	
	46		0·85083	0·1578	—	1318	1508	—	—	—	2583	1·714	—
cyclo-	25		0·77429	0·1774	871	1144	1310	1570	1778	1874	2266	1·730	—
Hexane	37	(*a*)	0·76297	0·1748	—	1153	1316	—	—	—	2271	1·726	1·727
		(*b*)	—	—	—	1150	1313	—	—	—	2267	1·726	
	50	(*a*)	0·75151	0·1722	—	1157	1322	—	—	—	2291	1·733	1·725
		(*b*)	—	—	—	1152	1316	—	—	—	2281	1·733	

The measurements given in Table 1 were made in the order: mercury-green, -yellow, and -violet. It is likely that for the green line either no correction or the (*a*) series correction should be applied, whilst for the violet line the full correction should be used, since in this case a relatively large number of slowly taken readings are required to give reasonable

accuracy. From the expanded results the order of error is judged to be $\leq \pm 3$ units for $\lambda = 5461$ and 5780 and about ± 15 for $\lambda = 4358$; from the curves of $[\alpha]$–t it would appear to be rather less than this, being 1—2 and up to 5 units respectively. In Table 2 are given the values of the slope of the curve $[\alpha]$–t as calculated for the (*a*) and the (*b*) series corrections, the latter being in parentheses.

TABLE 2.

Solvent	$[\alpha]_{5780}$–t		$[\alpha]_{5461}$–t		$[\alpha]_{4358}$–t	
CCl_4	1·47°	(1·01°)	1·34°	(1·02°)	4·04°	(3·9°)
Benzene	0·4	—	0·7	(0·25)	2·1	(0·8)
*cyclo*Hexane	0·65	(0·4)	0·6	(0·3)	0·95	(0·55)

DISCUSSION

The effect of a rise in temperature on the specific rotatory power of homogeneous liquids is generally to cause a reduction in their rotatory power when their dispersion is simple. Kauzman, Walter, and Eyring (*Chem. Reviews*, **1940**, **26**, 373, 381) have discussed this effect from the theoretical point of view and conclude that in simple substances such as 2-chlorobutane there should be a considerable decrease in the numerical value of the rotatory power with rise in temperature. However, they point out that the optical rotation of simple substances generally decreases only slightly with rising temperature. They also consider that the first- and second-order contributions to the rotatory power (arising from groups respectively far from and close to the chromophoric group) may be of opposite sign. A rise in temperature might thus result in an increase in the rotatory power if the first- and second-order contributions are affected to a different extent. It is noteworthy in this connection that the rotatory power of (−)-menthol shows a maximum value of the rotatory power at 60° although the substance exhibits simple dispersion (Kenyon and Pickard, *J.*, 1915, **107**, 35).

In their discussion no account is taken of the fact that rotatory power is to be considered as the resultant of several rotatory strengths and that not only the rotatory power but also the rotatory dispersion may be markedly affected by temperature changes (Balfe, Hargreaves, and Kenyon, *J.*, **1950**, 1861). The change of the rotatory dispersion of octan-2-ol (Hargreaves, *loc. cit.*) with temperature shows that the rotatory strengths of $-\overset{|}{\underset{|}{C}}H$, $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$, and $-\overset{|}{\underset{|}{C}}-OH$ absorption bands may be differently affected by temperature changes.

The dispersion ratios of solutions of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene vary only slightly with temperature. The variation is particularly small when the series (*a*) corrections are applied for $\lambda = 5461$ Å and the series (*b*) for $\lambda = 4358$ Å. There is clearly no loss in rotatory power accompanying a rise in temperature (within the range 25—50°), and a slight rise in rotatory power with rise in temperature would be the simplest explanation of the results here reported. (Details of the various corrections which must be applied are given in the Experimental section.) In view of the possibly subjective nature of measurements of optical rotatory power, the author attaches some importance to the fact that the density corrections were not applied until some weeks after the conclusion of the experiments. Although the increases in the rotatory power reported are only 0—10 times the observational error the general trend of the results is all in one direction, and it seems clear that, failing some unidentified error in the measurements, there must be a small rise in the optical activity of these solutions with rise in temperature. Since $\Omega = 3[\alpha]/(n^2 + 2)$, it seems clear that the rotivity (Ω) will rise with temperature rather more than $[\alpha]$.

It is interesting that 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene should show this effect since it has a rather rigid structure. This implies that this small observable rise in the rotatory power is not due to rotational isomers or freedom of configuration but is associated with the field within the molecule.

EXPERIMENTAL

Polarimeter.—A Bellingham and Stanley variable half-shadow two-field instrument was used, fitted with a ground glass in the aperture at the light end. Usually about 6 rather quick

readings were taken for the green and yellow lines, and 10—20 laborious readings for the violet line.

Polarimeter Tubes.—These were of fused silica with integral end-plates. The expansion of the tubes is negligible compared to other factors. A small correction was necessary for the rotatory power of the end-plates. This correction was determined as 0·05° for the mercury-green line, and the correction for other wave-lengths was calculated by means of the values for the rotatory dispersion of quartz (International Critical Tables, McGraw-Hill, New York, 1929, **6**, 342). The variation of the rotatory power of the end-plates with temperature for $\lambda = 5461$ Å was found to be less than 0·01°. This is in agreement with the values for quartz given in the I.C.T. (p. 343) which show a variation of $< +0{\cdot}0004°$ for a rise from 0° to 50°. This comparison would not be strictly valid, however, if the rotatory power of the end-plates were due to strain, since an increase of temperature might be expected to increase the strain. The rotatory power of the end-plates is of opposite sign to that of the solutions, so if temperature were to have any effect it would be expected partially to mask the increase in the rotatory power of the solutions.

TABLE 3. *Actual rotations α, and tube and evaporation corrections.*

Solvent ($l = 2$)	t	Wave-length, Å: 6438	5780	5461	5086	4800	4678	4358	α^{25}_{5461} corr. for tube: before heating	after heating	Evaporation correction: Series (*a*)	Series (*b*)
CCl_4	25°	3·86°	5·01°	5·76°	6·84°	7·83°	8·31°	9·56°	—	—	—	—
	40	—	5·04	5·76	—	—	—	9·78	5·81°	5·87°	5·81 / 5·84	5·81 / 5·87
	51	—	—	5·79	—	—	—	9·79	5·87	5·88	5·81 / 5·87	5·81 / 5·88
Benzene	25	3·00	4·20	4·79	5·81	6·63	6·97	8·11	—	—	—	—
	37	—	4·17	4·77	—	—	—	8·09	4·84	4·88	4·84 / 4·86	4·84 / 4·88
	46 *	—	4·12	4·71	—	—	—	8·08	4·84	4·84	—	—
*cyclo*Hexane	25	3·06	4·02	4·60	5·51	6·24	6·58	7·96	—	—	—	—
	37	—	4·00	4·56	—	—	—	7·88	4·65	4·67	4·65 / 4·66	4·65 / 4·67
	50	—	3·97	4·53	—	—	—	7·86	4·67	4·70	4·65 / 4·68	4·65 / 4·70
Tube correction to be added to figures above		0·03	0·04	0·05	0·06	0·07	0·07	0·08				

* Run at 46° before 37° experiment.

Densities.—The decrease in the concentration of the active molecules with rise of temperature was calculated from the variation of the densities of the solvents with temperature (I.C.T., 1928, **3**, 28). The variation with temperature of the densities of 0·2% solutions of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene was assumed to be the same as that of the pure solvent. This assumption seems reasonable in view of the nature of the solute and solvent molecules.

Evaporation Corrections.—In Table 3 are given the actual values of α at different temperatures and the values of α^{25}_{5461} observed before and after heating to each higher temperature.

Temperature Control.—Water from a thermostat controlled to 0·2° was rapidly circulated. Temperature was measured by direct insertion of the thermometer into the active liquid.

The author thanks Dr. D. Muriel Hall for the loan of 0·1 g. of active 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene (for preparation, see Hall and Turner, *Chem. and Ind.*, 1953, 1177) and Professor E. E. Turner, F.R.S., for facilities for this work.

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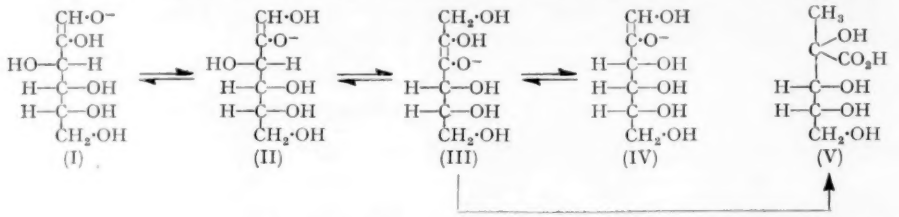
*The Degradation of Carbohydrates by Alkali. Part IV.** 1-O-*Methylfructose, Glucose, and Fructose.*

By J. Kenner and G. N. Richards.

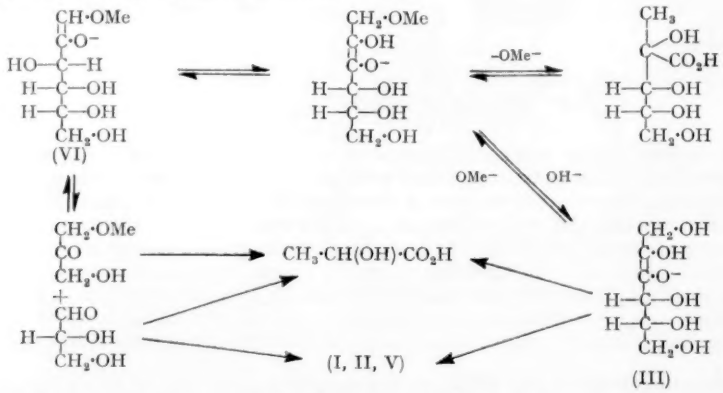
[Reprint Order No. 5054.]

1-*O*-Methylfructose is shown to yield α-D-glucosaccharinic acid on treatment with lime-water. The behaviour of glucose and fructose towards this reagent has also been examined.

It was emphasised in Part III * of this series that the presence of an *O*-alkyl or *O*-glycosyl group in the 3- or the 4-position of a glucose chain determines the type of saccharinic acid formation occasioned by the action of lime water on the compound. Further, Kiliani obtained D-glucosaccharinic acid (V) as the chief product of the action of lime-water on invert sugar at the room temperature (*Ber.*, 1882, **15**, 2953). This, as we may reasonably infer from the β-alkoxy- or -hydroxy-carbonyl mechanism operative in this type of reaction (cf. Corbett and Kenner, *J.*, 1953, 2245), arises from the anion of the 3-ketohexose (III), which is in equilibrium with those of glucose (I), fructose (II), and psicose (IV), but loses



a hydroxyl ion more readily than these do because the electronic flux towards $C_{(1)}$ is impeded less by the hydrogen atoms attached to it than are those towards $C_{(3)}$ and $C_{(4)}$ by the groups respectively attached to them.

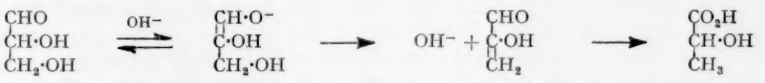


Observations on the presence of psicose in alkaline solutions of glucose have been recorded by Wolfrom, Lew, and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 1443), Hough, Jones, and Richards (*J.*, 1953, 2005), and Schneider and Erlemann (*Naturwiss.*, 1952, **39**, 160), and are also evidence of the presence of (III) in such solutions.

Consideration of these facts made a study of the behaviour of 1-*O*-methylfructose desirable. The compound is available by methylation and subsequent hydrolysis of 2 : 3-4 : 5-di-*O*-*iso*propylidenefructose (Ohle, *Ber.*, 1925, **58**, 2577; Glen, Myers, and Grant, *J.*, 1951, 2568), and on treatment with lime-water yielded α-D-glucosaccharinic acid (IV),

* Part III, *J.*, 1954, 278.

thus indicating wider validity for the generalisation of Part III. The acid was accompanied, however, by a considerably larger proportion of lactic acid. In addition, there was chromatographic evidence of the formation of very small quantities of other acids, with R_F values corresponding to those of *iso*- and *meta*-glucosaccharinic acid. Similarly, and confirmatory of the above scheme, there was evidence of the presence at intermediate stages of the anions, not only of 1-*O*-methylfructose (VI) but also of psicose (and possibly of its 1-*O*-methyl derivative), glucose, fructose, and mannose. The alternative possible modes of formation are shown in the scheme. The predominance of lactic acid over saccharinic acid here recorded is also familiar in the degradation of glucose and fructose by alkali and is perhaps due to the greater simplicity of a reversible aldol reaction in comparison with the elimination of anion on which saccharinic acid formation depends, though it must be realised that this latter is exactly reproduced in the ultimate stages of lactic acid formation :

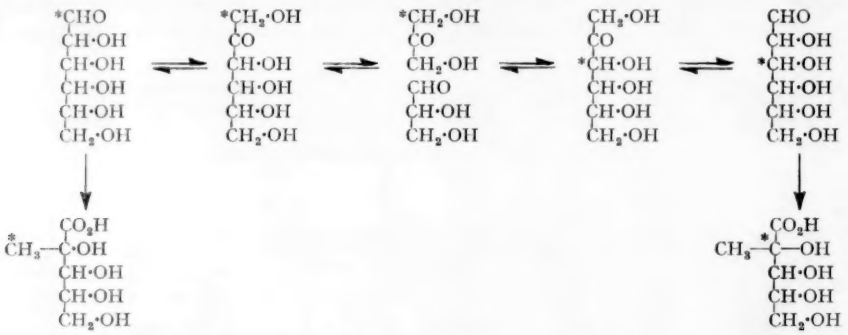


We have now also followed the decomposition of glucose and fructose themselves by lime-water. The apportionment of the total acidic products, as measured by decrease in alkalinity of the solutions, between lactic and saccharinic acids depended on lactonisation

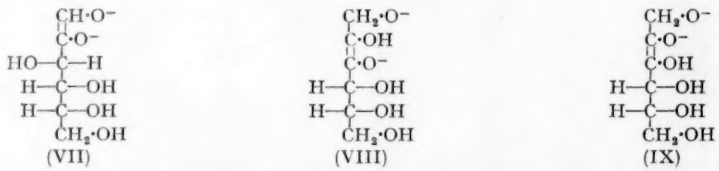
Time (hr.)	Acid equivs. per mole of hexose	Total hexoses (mg.)	Ketose (mg.)	Aldose (mg.)	Paper chromatography † G	F	P	T	Sacc. acids
			Glucose (0·316 *g.*) *in* 0·0375N-*lime-water* (100 ml.).						
0	0	316	0	316	3	—	—	—	—
0·25	0	316	9·0	307	3	0·5	—	—	—
0·55	0	316	10·2	306	3	0·5	—	—	—
1·0	0	315	14·4	302	3	0·5	—	—	—
2·0	0·017	318	22·6	293	3	1	—	—	—
3·0	0·014	317	30·4	286	3	1	—	—	—
7·25	0·057	308	64·4	244	3	2	0·5	—	—
10	0·100	304	90·0	214	3	2	0·5	—	0·5
24	0·279	267	111	156	2	3	1	0·5	1
27	0·328	259	105	154	2	3	1	0·5	1
31	0·367	250	105	145	2	3	1	0·5	1
48	0·580	203	89·0	114	2	2	1	0·5	1
72	0·789	161	71·0	90	2	2	1	0·5	2
168	1·24	83	23·4	60	1	1	0·5	—	3
218	1·37	55	14·4	41	1	0·5	0·5	—	3
338	1·525	31	8·0	23	1	0·5	—	—	3
			Fructose (0·316 *g.*) *in* 0·0404N-*lime-water* (100 ml.).						
0	0	316	316	0	—	3	—	—	—
0·25	0·014	316	307	9	0·5	3	—	—	0·5
0·5	0·023	317	297	18	0·5	3	—	—	0·5
0·75	0·034	314	288	26	0·5	3	—	—	0·5
1·0	0·037	311	278	33	0·5	3	—	—	0·5
1·5	0·051	311	258	53	1	3	—	—	0·5
2·0	0·071	306	248	58	1	3	—	—	0·5
3·0	0·100	302	217	85	2	3	—	—	0·5
4·0	0·116	296	208	88	2	2	0·5	—	0·5
5·5	0·159	292	189	103	2	2	0·5	—	0·5
7·5	0·219	280	162	118	2	2	0·5	—	0·5
24	0·593	199	74	125	2	1	1	0·5	1
31·5	0·684	176	60·5	116	2	1	1	0·5	1
48	0·860	140	43	97	2	1	0·5	0·5	2
131	1·25	70	18	52	1	0·5	—	0·5	3
179	1·39	52	12·5	39	1	0·5	—	0·5	3
299	1·57	22	6	16	0·5	0·5	—	—	3
400	1·615	15	*	*	0·5	0·5	—	—	3
525	1·63	8	*	*	0·5	—	—	—	3

* Not determined. † Numbers denote relative intensity, 3 denoting the greatest.
G, glucose; F, fructose + mannose; P, psicose; S, saccharinic acids; T, supposed triose.

of the latter and ascription of the residual acidity to lactic acid (cf. Bamford, Bamford, and Collins, *Proc. Roy. Soc.*, 1950, *A*, **204**, 85). Alternatively, but less reliably owing to the need to use an additional set of experimental results, the relative proportions were deduced from the consideration that each molecule of hexose can afford either one of saccharinic acid, or two of lactic acid, the amount of (±)-αγ-dihydroxybutyric acid formed being very small. As in earlier papers of this series the actual consumption of hexose was determined by the Hagedorn–Jensen method, and, in addition, the proportion of ketose present at any time was estimated colorimetrically by means of resorcinol and hydrochloric acid (cf. Gray, *Analyst*, 1950, **75**, 314). Finally, chromatographic analysis was applied to the reactant solution at each stage. The Table shows the results obtained at 25°. The lag observed in the development of lactic acid from glucose, as compared with fructose, supports the generally accepted view that fission of the six-carbon chain proceeds, not as was suggested by Wohl (*Z. angew. Chem.*, 1907, **20**, 1169) independently in the case of glucose through 3-deoxyglucosone, but in each case through the ketose. As an evident consequence of the reversibility of the reaction, an isotopic carbon atom originally in position 1 can appear in the equilibrium mixture partly in position 1 and partly in position 3, so that in the D-glucosaccharinic acid ensuing from the further action of lime-water, the isotope will occur in one or other of the positions shown. This has been



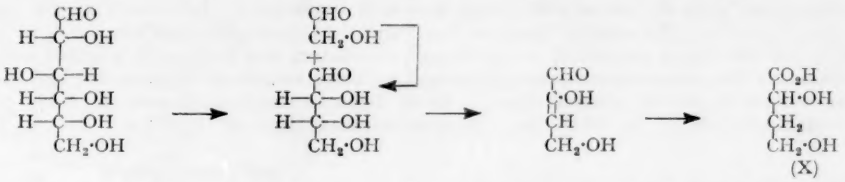
recently confirmed by Sowden (*J. Amer. Chem. Soc.*, 1953, **75**, 2788), but his inference, that the mechanism of the saccharinic acid formation is thereby rendered doubtful, is clearly not permissible. Rather the results support the suggestion that conversion of glucose into galactose through fission into three-carbon units is possible (Kenner, *Nature*, 1935, **135**, 506). On the other hand such a process is inhibited by substitution in the 4-*O*-position, and the occurrence of this in maltose, lactose, cellobiose, and the corresponding oligosaccharides may be Nature's device for safeguarding the storage of glucose until its due use is required.



(VII) (VIII) (IX)

There can evidently be no sharp line of division between the effects of strong and of dilute alkali and we have already referred to indications of the presence of the meta- and *iso*-acids among the products of the action of lime-water on methylfructose. These were more pronounced in the experiments on fructose itself, and Nef found them to be the chief saccharinic products when glucose is treated with 8N-sodium hydroxide. These conditions should favour the existence of doubly charged anions, among which (VII) might be expected to predominate and yield metasaccharinic acid; (VIII) should be unreactive, but (IX) could furnish *iso*saccharinic acid.

Lactic acid was the chief product of the reaction and is generally regarded as arising primarily from dealdolisation between $C_{(3)}$ and $C_{(4)}$ on the glucose chain. Clearly, however, a similar process could occur between $C_{(2)}$ and $C_{(3)}$, yielding glycollaldehyde and a tetrose, which by further action of the alkali could be converted into the four-carbon metasaccharinic system, (±)-αγ-dihydroxybutyric acid (X), which was also an important product.



Nef (*loc. cit.*) demonstrated that the deoxytetronic acid is also formed from glycollaldehyde, presumably, as indicated, through the tetrose. Mention should also be made of a kinetic study of these reactions by Bamford, Bamford, and Collins (*loc. cit.*).

Experimental

1-*O*-Methylfructose (Ohle, *loc. cit.*; Glen, Myers, and Grant, *loc. cit.*) was freed from traces of fructose on a cellulose column (cf. Kenner and Richards, *loc. cit.*). The syrupy product, $[\alpha]_D^{20}$ −50·2° (*c*, 1 in MeOH), was characterised by its p-*nitrophenylhydrazone*, orange needles, m. p. 166° (Found: N, 12·8. $C_{13}H_{19}O_7N_3$ requires N, 12·8%).

A solution of the ketose (6·03 g.) in oxygen-free water (100 ml.) was kept at room temperature with calcium hydroxide (5 g.) for 14 days, with occasional agitation. After filtration the solution was freed from calcium ions by means of Amberlite resin IR-120, and evaporated under reduced pressure to a thin syrup which was extracted continuously with ether for 24 hr. Concentration of the extract yielded long needles of α-D-glucosaccharinolactone (1·25 g.); recrystallised from acetone, this had m. p. 164·5—165°, $[\alpha]_D^{21}$ +92·8° (*c*, 2 in H_2O) (Found: C, 44·3; H, 6·3. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2%). Nef (*loc. cit.*) reported m. p. 160°, $[\alpha]_D^{20}$ +93·28°.

The remainder of the ethereal extract, after removal of the saccharinolactone, was evaporated to dryness and part of the residual syrup (0·242 g. from 3·98 g.) was dissolved in water, neutralised with sodium hydroxide (final vol. 10 ml.), and heated under reflux with a solution of 4-bromophenacyl bromide (0·7 g.) in ethanol (10 ml.) for 1 hr. Fractional precipitation of the product by water from the resulting solution yielded 4-bromophenacyl lactate, m. p. and mixed m. p. 111—113°.

In a kinetic study of the decomposition of 0·708 g. in oxygen-free lime-water (250 ml.; 0·0419N) at 25°, the total acidic products were estimated by back-titration of excess of sulphuric acid, and the saccharinic acid proportion by a development of the method of Bamford, Bamford, and Collins (*loc. cit.*) whereby the neutralised solution was brought to 0·02N with sulphuric acid and boiled for 15 min., and the decrease in acidity determined by titration with potassium hydroxide (for correction factor, see below). Identification and rough visual estimation of carbohydrates by paper chromatography, with butanol–pyridine–water (3 : 2 : 1·5) solvent (A), gave results as follows:

(*a*) Glucose (R_F 0·28), responsive to *p*-anisidine, and silver nitrate–sodium hydroxide, but not to naphtharesorcinol spray. These tests gave negative results after a deionised solution of the mixture (1 ml. at 40° for 20 hr.) had been treated with glucosedehydrogenase (for which we were indebted to Dr. M. V. Lock). This treatment, however, yields a product corresponding to gluconic acid ($R_F < 0·1$).

(*b*) Fructose + mannose (R_F 0·31); mainly the former as judged by relative responses to naphtharesorcinol, *p*-anisidine, and silver nitrate–sodium hydroxide sprays.

(*c*) Psicose (R_F 0·375 in agreement with an authentic sample, kindly supplied by Professor J. K. N. Jones), yielding pink colours with *p*-anisidine and naphtharesorcinol sprays.

(*d*) 1-*O*-Methylfructose (R_F 0·475), coloured brown by *p*-anisidine and pink by naphtharesorcinol sprays.

(*e*) 1-*O*-Methylpsicose (?) (R_F 0·54), with colour reactions as (*d*).

(*f*) A monomethyltriose (?) (R_F 0·74); for methylglyoxal R_F 0·85 was found.

The annexed table summarises the results.

A sample of the solution remaining after completion of the reaction with lime-water was shaken with excess of Amberlite resin IR-120 and then subjected to paper chromatography with butanol–ethanol–acetic acid–water (45 : 5 : 1 : 49) (solvent B.) Lactones were subsequently detected by spraying the paper with hydroxylamine followed by acidic ferric chloride as described by Abdel-Akher and Smith (*J. Amer. Chem. Soc.*, 1951, **73**, 5859). Authentic samples of β-glucometasaccharinolactone, α-glucoisosaccharinolactone, and α-D-glucosaccharinolactone gave R_F values 0·35, 0·455, and 0·56 respectively; lactic acid gave a faint reaction (R_F 0·71). The solution from the treatment of 1-*O*-methylfructose was shown in this way to contain a large amount of α-D-glucosaccharinolactone and lactic acid, together with a faint trace of the α-gluco*iso*saccharinolactone and β-glucometasaccharinolactone and also three other lactones in similar amount, thought to be β-glucoisosaccharinolactone (R_F 0·42), β-D-glucosaccharinolactone (R_F 0·61), and α-gluco*meta*saccharinolactone (R_F 0·28).

Time (hr.)	Total acid (eq./mole)	Sacc. acid (eq./mole)	Lactic acid (eq./mole)	Paper chromatography						
				a	*b*	*c*	*d*	*e*	*f*	Sacc. acids
0·55	0·082	0·015	0·067	—	—	—	4	—	—	—
1·0	0·127	0·023	0·104	—	—	—	4	0·5	—	—
2·0	0·211	0·037	0·174	0·5	0·5	0·5	4	0·5	0·5	—
3·0	0·310	0·053	0·257	×	×	×	×	×	×	×
4·0	0·401	0·060	0·341	0·5	1	0·5	3	1	0·5	—
5·0	0·466	0·068	0·398	×	×	×	×	×	×	×
6·0	0·531	0·075	0·456	0·5	1	1	3	1	1	1
7·5	0·628	0·119	0·509	×	×	×	×	×	×	×
24·5	1·18	0·189	0·99	1	1	1	2	1·5	0·5	2
55	1·41	0·191	1·22	—	0·5	—	1	0·5	—	2
97	1·54	0·197	1·34	×	×	×	×	×	×	×
121	1·60	0·222	1·38	×	×	×	×	×	×	×
144	1·61	0·229	1·38	×	×	×	×	×	×	×
169	1·65	0·242	1·41	×	×	×	×	×	×	×
193	1·66	0·268	1·39	×	×	×	×	×	×	×
318	1·67	0·264	1·41	×	×	×	×	×	×	×
482	1·67	0·268	1·40	—	—	—	—	—	—	3

— Not detected. × Not examined.

Action of Lime-water on Glucose and Fructose.—As a supplement to Kiliani's work (*loc. cit.*), a solution of glucose (25·5 g.) in saturated oxygen-free lime-water (500 ml.), with calcium hydroxide in suspension, was maintained with occasional shaking for 500 hr. at 20° ± 1°. The filtered solution (then only slightly reducing) was again filtered after treatment with an aqueous solution (200 ml.) of oxalic acid dihydrate (20 g.). After concentration of this filtrate under reduced pressure to 500 ml., residual calcium ions were removed by means of Amberlite resin IR-120 (150 g.), and the solution, with washings, was concentrated to a thin syrup. The distillate at this stage contained $7·6 \times 10^{-3}$ equiv. of volatile acid including $5·6 \times 10^{-3}$ equiv. of formic acid (determined according to Evans and Hass, *J. Amer. Chem. Soc.*, 1926, **48**, 2705). Continuous extraction of the syrup with ether for 48 hr. over a mixture of ether, water, and zinc carbonate furnished zinc lactate (14·4 g.) (cf. Evans and Hass, *loc. cit.*) (Found : H_2O, 30·6. Calc. for $C_3H_5O_3Zn_{\frac{1}{2}},3H_2O$: H_2O, 30·5. Found, on anhyd. salt, Zn, 27·0. Calc. for $C_3H_5O_3Zn_{\frac{1}{2}}$: Zn, 26·9%). The recovered residual yellow syrup (8·3 g.), with slight reducing properties, partly crystallised after several weeks at 0°. The separated solid, twice recrystallised from acetone (yield 1·05 g.), showed m. p. 164·5—165°, $[\alpha]_D^{20}$ +92·8° (*c*, 2 in H_2O) (Found : C, 44·3; H, 6·3. Calc. for $C_6H_{10}O_5$: C, 44·4; H, 6·2%). Data from quantitative experiments are recorded in the introduction. Acidic products were determined as in the case of 1-*O*-methylfructose, and aldose–ketose determinations as described in Part III. Chromatographic identification of carbohydrates depended on comparison with known materials in respect of R_F values. That of a supposed triose was 0·74 (solvent A). Similarly the lactones present in an equilibrium solution of glucose, or of fructose, in lime-water, after shaking with Amberlite resin IR-120, were identified (solvent B) as chiefly α-D-glucosaccharinolactone (R_F 0·56), with α-D-gluco*iso*saccharinolactone (R_F 0·42), and β-D-glucometasaccharinolactone (R_F 0·28), together with the isomers tentatively identified in the product from 1-*O*-methylfructose.

In addition to the quantitative studies cited in the introduction, others were made, based on the modified lactonisation procedure of Bamford, Bamford, and Collins (*loc. cit.*) with a correction factor of 1·15 based on a preliminary experiment with authentic α-D-glucosaccharinolactone. The same factor was applied to the corresponding experimental results

obtained with 1-*O*-methylfructose. The following results were thus obtained with solutions of glucose (0·788 g.) and fructose (0·783 g.) respectively, each in oxygen-free lime-water (250 ml.; 0·0396N) at 25°.

	Glucose.			*Fructose.*		
Time (hr.)	Total acid (eq./mole)	Sacc. acid (eq./mole)	Lactic acid (eq./mole)	Total acid (eq./mole)	Sacc. acid (eq./mole)	Lactic acid (eq./mole)
0·25	0	*	0	0·013	0	0·013
0·5	0	*	0	0·023	0	0·023
1·0	0	*	0	0·046	0·003	0·043
2·0	0·003	*	0·003	0·072	0·013	0·059
3·0	0·007	*	0·007	0·01	0·02	0·08
4·0	0·023	0	0·023	0·13	0·03	0·10
5·0	0·030	0·003	0·027	0·16	0·03	0·13
6·0	0·047	0·007	0·040	0·20	0·04	0·16
7·0	0·064	0·013	0·051	0·22	0·045	0·18
24	0·37	0·05	0·32	0·56	0·10	0·46
49	0·69	0·10	0·59	0·82	0·13	0·69
193	1·34	0·28	1·06	1·34	0·32	1·02
529	1·58	0·28	1·30	1·52	0·33	1·19
625	1·62	0·28	1·34	1·52	0·32	1·20

* Not determined

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British Rayon Research Association,
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The Degradation of Carbohydrates by Alkali. Part V. Lactulose, Maltose, and Maltulose.*

By W. M. Corbett and J. Kenner.

[Reprint Order No. 5055.]

The behaviour of lactulose, maltose, and maltulose towards lime-water at 25° accords with the scheme put forward earlier (*J.*, 1953, 2245).

It was shown in Part II (Corbett and Kenner, *J.*, 1953, 2245) that lactose suffers degradation by lime-water to a mixture of α- and β-*iso*saccharinic acid and galactose. Conversion of aldose into ketose was postulated as the first step. Accordingly lactulose has now been prepared by a method essentially that of Hudson and Montgomery (*J. Amer. Chem. Soc.*, 1930, **52**, 2101) but so reinforced that the product might satisfy chromatographic tests not then available.

The action of lime-water on lactulose has been studied by Isbell (*J. Res. Nat. Bur. Stand.*, 1941, **26**, 35), who attributed an observed increase in dextrorotatory power solely to partial reversion of the ketose to lactose. However, our examination of the various aspects of the reaction has shown it to correspond in detail with the degradation of lactose but to proceed, as expected, more rapidly.

In order further to substantiate the scheme of degradation put forward for lactose and lactulose, we also studied maltose and maltulose, with the expected results. Maltose gave glucose and α- and β-*iso*saccharinic acid as initial products, whilst the rate of decomposition of maltulose so substantially exceeded that of maltose that only in experiments on a larger scale could its formation be detected chromatographically during the degradation of maltose. Similarly no maltose, resulting from a Lobry de Bruyn transformation, was observable during the degradation of maltulose. By contrast the slower rates of degradation of lactose and lactulose permitted the detection of each during the degradation of the other.

Another difference between the reactivities of 4-*O*-α-glucosyl- and 4-*O*-β-galactosyl-fructose lay in that, whereas in the former case the observed decrease in alkalinity of its solution in lime-water in the early stages of the reaction afforded a measure of *iso*saccharinic

* Part IV, preceding paper.

acid formation consistent with the other experimental data, the value so deduced in the latter case was excessive. We shall later record a similar experience with cellobiose.

A time-lag in the onset of decomposition was observed with each aldose, corresponding to the necessary preliminary genesis of the ketoses and to the similarly delayed action on glucose (Kenner and Richards, preceding paper).

Finally, a detailed examination of the products from a large-scale experiment on the degradation of lactose showed it not to afford a satisfactory mode of preparing pure galactose owing to simultaneous formation of other hexoses not easily separable from it.

Experimental

Lactulose.—The amorphous product (18 g.) prepared from lactose (120 g.) by the adoption of Montgomery and Hudson's procedure (*J. Amer. Chem. Soc.*, 1930, **52**, 2101) described by the National Bureau of Standards (Circular C.440, Washington, 1942, p. 467) was freed from monoses by elution of these with water from the adsorbate on a charcoal–Celite column (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677). The disaccharide was recovered by elution with 5% aqueous ethanol. After removal of ions by a mixture of resins [Amberlite IR-120(H) and IR-4B(OH)], the chromatographically satisfactory ketose was still amorphous, $[\alpha]_D^{23}$ (equil.) −49·1° (*c*, 1·140 in H_2O); values of −51·5° and −50·7° are recorded by the respective authorities cited above.

Table 1 summarises the observations made with a solution (50 ml.) of the ketose (0·3946 g.) in saturated oxygen-free lime-water (0·042N) at 25°, determinations of monoses and saccharinic acids being carried out as in the case of lactose (Corbett and Kenner, *loc. cit.*; Corbett, *Chem. and Ind.*, 1953, 1285) and calculated on the basis of formation of one molecular proportion of each from one of the ketose. As in all other cases studied the monose content reached a maximum and towards the end of the degradation was less than the disaccharide degraded owing to the further action of the lime-water on the former to give excess of acid.

Maltose and Maltulose.—Tables 2 and 3 in respect of the behaviour of maltose (0·8616 g.) in oxygen-free lime-water (100 ml.; 0·044N) and of maltulose (0·4266 g.) in oxygen-free lime-water (50 ml., 0·041N) are appended. The preparation of the ketose in a chromatographically

Table 1. *Degradation of lactulose by saturated lime-water at 25°.*

Time (hr.)	α_D	Lactulose decompd. (%)	Monoses formed (%)	Sacc. acids (%)	Paper-chromatography *				
					lactulose	lactose	galactose	tagatose	sacc. acids
0·1	−0·06°	1·7	1·2	0·0	3	—	—	—	—
0·5	0·06	2·5	2·4	6·9	3	—	1	—	—
1	0·05	6·4	7·2	9·1	3	—	1	—	—
2	0·03	15·5	13·2	16·2	3	1	1	—	1
3	0·01	18·3	22·8	14·7	3	1	1	—	1
5	+0·01	25·0	33·7	29·2	3	1	1	1	1
6	0·01	29·5	36·7	37·4	3	1	1	1	1
24	0·03	66·8	58·8	63·8	2	1	2	1	2
30	0·03	74·4	66·7	71·1	2	1	2	1	2
48	0·01	81·7	67·5	84·5	1	1	2	1	2
54	0·01	83·9	69·3	82·4	1	1	2	1	2
72	0·01	88·1	68·1	85·5	1	1	2	1	2
96	0·01	89·2	65·0	81·2	1	1	2	1	2
168	0·01	89·9	63·2	82·4	1	1	2	1	2

* Numerals here and in Tables 2 and 3 denote relative intensity, 3 denoting the greatest intensity.

Table 2. *Degradation of maltose by saturated lime-water at 25°.*

Time (hr.)	α_D	Maltose decompd. (%)	Monoses formed (%)	Total acids produced (%)	Paper chromatography				
					maltose	glucose	fructose	mannose	sacc. acids
0·5	+0·48°	0·0	0·0	0·0	3	—	—	—	—
1	0·46	0·0	0·0	0·0	3	—	—	—	—
2	0·43	7·5	4·8	7·6	3	1	—	—	—
4	0·36	16·5	8·6	21·0	3	1	—	—	—
6	0·31	36·0	22·4	31·4	3	1	—	—	1
24	0·10	83·4	71·5	100·0	1	2	1	1	2
48	0·04	91·7	78·2	126·8	1	2	1	1	2
120	±0·00	100·0	65·5	171·0	—	1	1	1	2
144	±0·00	100·0	67·5	174·0	—	1	1	1	2
192	±0·00	100·0	61·5	188·0	—	1	1	1	2
288	±0·00	100·0	56·2	199·0	—	1	1	—	2

TABLE 3. *Degradation of maltulose by saturated lime-water at 25°.*

Time (hr.)	α_D	Maltulose decompd. (%)	Monoses formed (%)	Total acids produced (%)	Paper chromatography: maltulose	glucose	fructose	mannose	sacc. acids
0·25	+0·06°	12·9	18·4	5·2	3	1	—	—	—
1	0·06	31·5	36·1	19·9	3	1	—	—	1
2	0·05	50·6	50·2	37·7	3	1	—	—	1
3	0·06	59·3	56·3	53·5	3	2	—	—	1
4	0·04	70·7	68·6	61·8	2	2	—	—	1
5	0·03	78·0	77·5	66·1	2	2	—	—	2
6	0·04	80·5	75·2	71·5	2	2	—	—	2
7	0·03	82·5	78·0	73·4	1	2	1	—	2
24	0·01	95·5	88·7	94·3	1	2	2	1	2
31	±0·00	97·0	87·0	99·0	1	2	2	1	2
48	0·00	100·0	88·0	108·2	—	2	2	1	2
72	0·00	100·0	73·0	122·0	—	2	2	1	2

satisfactory state followed the lines indicated in the case of lactulose and the product had $[\alpha]_D^{19}$ (equil.) +56·2° (*c*, 0·499 in H_2O). Peat, Roberts, and Whelan (*Biochem. J.*, 1952, **51**, xvii) and Hough, Jones, and Richards (*J.*, 1953, 2005) respectively observed $[\alpha]_D$ +52·8° (in H_2O) and +58—64° (*c*, 1·58 in H_2O).

Isolation of the Degradation Products from Maltose.—A solution (5 l.) of maltose (50·0 g.) in saturated oxygen-free lime-water was kept at 20—23° for 65 hr. before it was neutralised with cold aqueous oxalic acid, filtered, and concentrated at 60° to *ca.* 500 ml. The sparingly soluble calcium α-*iso*saccharinate (7·20 g., 24·7%) which separated was converted quantitatively into α-*iso*saccharin, having m. p. 94—96°, $[\alpha]_D^{20}$ +60·3° (*c*, 4·21 in H_2O), after one crystallisation from ethyl acetate (Found: C, 44·3; H, 6·3. Calc. for $C_6H_{10}O_5$: C, 44·5; H, 6·2%). Nef (*Annalen*, 1910, **376**, 52) gave m. p. 96°, $[\alpha]_D^{20}$ +61·9°.

After quantitative precipitation of calcium, as oxalate, from the mother-liquors these were eluted from a column of Amberlite IR-4B resin (100 g.). The combined eluate and aqueous washings (1 l.) were concentrated to a syrup (24·67 g., 94·0% for monoses), shown by paper chromatography to contain essentially glucose and fructose, with small amounts of maltose, maltulose, and psicose (?), and traces of saccharinic acids. The dried syrup (from which glucose phenylosazone, m. p. and mixed m. p. 203—205°, was prepared in good yield) was extracted with dry acetone; concentration of the extract afforded a mixture of *iso*saccharins (1·56 g.).

Finally the basic resin was eluted with 0·1M-sodium carbonate (750 ml.) followed by water (500 ml.), the combined eluates then being stirred for several hours with Amberlite IR-120 resin (200 g.) and filtered. The acidic resin was washed with water (3 × 250 ml.), and the washings were combined with the filtrate and concentrated under reduced pressure to a dark syrup (3·487 g., 15%). This, when neutralised with lime-water, treated with charcoal, filtered and concentrated, yielded a syrup which solidified on trituration with alcohol. The calcium salts (2·831 g.) thus obtained were heated with water (5 ml.) and then kept at 0° for several hours before removal of the sparingly soluble calcium salt (0·548 g.). This was calcium lactate from which was prepared the brucine salt, m. p. 192—199°, $[\alpha]_D^{22}$ −29·0° (*c*, 1·79 in H_2O) (Found: N, 5·9. Calc. for $C_{26}H_{32}O_7N_2$: N, 5·8%). Nef (*loc. cit.*) gives m. p. 210°, $[\alpha]_D^{20}$ −29·05°. To the filtrate alcohol was added in portions to give the following fractions: from 54% alcohol, a white amorphous powder (0·049 g.), $[\alpha]_D^{23}$ −2·1° (*c*, 0·49 in H_2O); from 61% alcohol, 0·031 g., $[\alpha]_D^{23}$ ±0·00° (*c*, 0·31 in H_2O); from 70% alcohol, *calcium* β-iso*saccharinate* (0·365 g.), $[\alpha]_D^{23}$ +3·1° (*c*, 0·96 in H_2O) (Found: Ca, 10·7. $C_{12}H_{22}O_{12}Ca$ requires Ca 10·1%); from 82% alcohol, further calcium β-*iso*saccharinate (0·334 g.), $[\alpha]_D^{23}$ +2·2° (*c*, 1·39 in H_2O), from which was prepared brucine β-*iso*saccharinate, m. p. and mixed m. p. 190—198°, $[\alpha]_D^{21}$ −22·0° (*c*, 1·81 in H_2O) [Nef (*loc. cit.*) gives m. p. 200—210°, $[\alpha]_D^{20}$ −21°]; from 100% alcohol, further calcium β-*iso*saccharinate (0·863 g.), $[\alpha]_D^{20}$ +2·8° (*c*, 1·39 in H_2O) (Found: Ca, 10·1%). A solution of this salt, after the removal of calcium ions by Amberlite IR-120 resin, gave $[\alpha]_D^{22}$ +8·5° (*c*, 0·93 in H_2O), calculated for β-*iso*saccharin; Nef (*loc. cit.*) gives $[\alpha]_D^{22}$ *ca.* +6° for a crude sample of the β-*iso*saccharin. Crystalline β-*iso*saccharin could not be obtained from the purified calcium salt.

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THE BRITISH RAYON RESEARCH ASSOCIATION,
BARTON DOCK ROAD, URMSTON, NR. MANCHESTER. [*Received, January 23rd*, 1954.]

Intramolecular Acylation. Part II. The Ring Closure of Some β-Substituted β-1-Naphthylpropionic Acids.*

By M. F. Ansell and A. M. Berman.

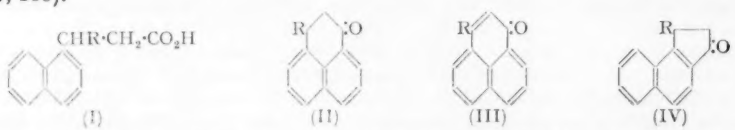
[Reprint Order No. 5074.]

The ring closure of each of four β-substituted β-1-naphthylpropionic acids by the action of anhydrous hydrogen fluoride yields a mixture of the corresponding 3-substituted perinaphthan-1-one, 3-substituted perinaphthen-1-one, and 3-substituted 4 : 5-benzindan-1-one.

In Part I * it was shown that cyclisation of α-alkyl-substituted β-1-naphthylpropionic acids gives a mixture of the corresponding 2-substituted perinaphthan-1-one and 2-substituted 4 : 5-benzindan-1-one. In an attempt to establish the generality of these results four β-alkyl-substituted β-1-naphthylpropionic acids (I), prepared by the general method of Bachmann and Edgerton (*J. Amer. Chem. Soc.*, 1940, **62**, 2219) outlined below, were cyclised. One of these acids, β-1-naphthylbutyric acid (I; R = Me), has been previously

$$1\text{-}C_{10}H_7\cdot COR \longrightarrow 1\text{-}C_{10}H_7\cdot CHR\cdot OH \longrightarrow 1\text{-}C_{10}H_7\cdot CHRBr \longrightarrow 1\text{-}C_{10}H_7\cdot CHR\cdot CH(CO_2Et)_2 \longrightarrow 1\text{-}C_{10}H_7\cdot CHR\cdot CH_2\cdot CO_2H.$$

cyclised by Boekelheide and Larrabee (*ibid.*, 1950, **72**, 1243) and Lock and Gergely (*Monatsh.*, 1948, **79**, 521), using anhydrous hydrogen fluoride. In both cases the only isolated product was 3-methylperinaphthan-1-one (II; R = Me). On repeating the experiment and chromatographing the crude product, we have isolated in addition 3-methyl-4 : 5-benzindan-1-one (IV; R = Me) together with a small amount of 3-methylperinaphthen-1-one (III; R = Me). The latter compound has been previously prepared by the action of piperidine on 1 : 8-diacetylnaphthalene (Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159).



(I) (II) (III) (IV)

The formation of perinaphthen-1-ones by the action of anhydrous hydrogen fluoride on β-1-naphthylpropionic acids has not been previously recorded, although it has been observed that the products are often yellow (Part I; Boekelheide and Larrabee, *loc. cit.*; Fieser *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 1855, 2335), probably owing to contamination with the corresponding perinaphthen-1-one. Cyclisation of β-1-naphthylpropionyl chloride with aluminium chloride in nitrobenzene does however give perinaphthen-1-one (von Braun, Manz, and Reinsch, *Annalen*, 1929, **468**, 277). This reaction presumably involves dehydrogenation of the first formed perinaphthan-1-one, for we have found that 3-methyl- and 3-ethyl-perinaphthan-1-one (see below) can be dehydrogenated to the corresponding perinaphthen-1-one under these conditions.

Similar results were obtained in the cyclisation of β-1-naphthylvaleric acid (I; R = Et), 3-ethylperinaphthan-1-one (II; R = Et), 3-ethyl-4 : 5-benzindan-1-one (IV; R = Et), and 3-ethylperinaphthen-1-one (III; R = Et) being isolated. On cyclising 3-1′-naphthylhexanoic acid † (I; R = Pr^n) it was found that when the chromatography was carried out slowly (elution with light petroleum) considerable decomposition occurred on the column and only 24% of 3-*n*-propylperinaphthan-1-one (II; R = Pr^n) was isolated together with 14% of 3-*n*-propyl-4 : 5-benzindan-1-one (IV; R = Pr^n) and 4% of 3-*n*-propylperinaphthen-1-one (III; R = Pr^n). When the chromatography was carried out more rapidly (elution with light petroleum–ether) no decomposition occurred and the yields were respectively 75, 15, and 0·2%. It therefore appears that the perinaphthan-1-one was oxidised by atmospheric oxygen to the perinaphthen-1-one. It has been observed that perinaphthan-1-ones darken in contact with air.

* Part I, *J.*, 1954, 575. † Geneva nomenclature, $CO_2H = 1$.

The cyclisation of 3-1′-naphthylheptanoic acid (I; R = Bu^n) was analogous to that of the previous examples, yielding 3-*n*-butylperinaphthan-1-one (II; R = Bu^n), 3-*n*-butylperinaphthen-1-one (III; R = Bu^n), and 3-*n*-butyl-4 : 5-benzindan-1-one (IV; R = Bu^n).

Absorption maxima (mμ) *in ethanol.*

	Perinaphthan-1-one					Perinaphthen-1-one						4 : 5-Benzindan-1-one					
2-Me	(220)	248	320	330	—	—	—	—	—	—	—	250	274	283	294	332	344
3-Me	(220)	248	322	331	—	(225)	248	254	322	360	(382)	250	275	284	294	331	344
3-Et	(223)	(240)	250	320	331	(225)	248	254	322	360	(382)	250	274	284	294	331	344
3-Pr^n	(221)	250	322	331	—	(225)	248	256	322	360	(382)	250	274	284	294	332	344
3-Bu^n	(221)	248	322	332	—	(225)	250	256	324	360	(382)	250	275	284	294	331	344

The structures of the various cyclisation products were assigned on the basis of their ultra-violet absorption spectra, which fell into three distinct groups (see Table). Authentic samples were available of 2-methylperinaphthan-1-one and 2-methyl-4 : 5-benzindan-1-one (Part I), and the structure of 3-methylperinaphthen-1-one was known from its previous preparation. Additional evidence for the structures of the perinaphthen-1-ones was their formation of yellow solutions in hydrochloric acid (Cook and Hewett, *J.*, 1934, 365).

Experimental

In all reactions with anhydrous hydrogen fluoride " Polythene " beakers were used and the reactions carried out in the open under shelter. Light petroleum used had b. p. 60—80°. The perinaphthen-1-ones gave yellow solutions in hydrochloric acid and black precipitates of indeterminate m. p. with 2 : 4-dinitrophenylhydrazine.

Preparation of 1-*Acylnapthalenes.*—1-Acetylnaphthalene, see Baddeley, *J.* 1949, S 99; 1-propionylnaphthalene, see Kloetzel and Wildman, *J. Org. Chem.*, 1946, **11**, 390; 1-butyrylnaphthalene and 1-valerylnaphthalene were prepared in yields of 80 and 78% respectively by the method of Kloetzel and Wildman (*loc. cit.*; cf. Nunn and Henze, *ibid.*, 1947, **12**, 540).

*Preparation of Alkyl-*1-*naphthylcarbinols.*—The 1-acylnaphthalene (0·13 mole) was added to a suspension of lithium aluminium hydride (2 g., 0·05 mole) in dry ether (60 c.c.) at such a rate that the ether refluxed, and then heated under reflux for 30 min. The mixture, cooled in ice, was decomposed with water, and poured into 10% sulphuric acid (1 l.). The ethereal layer was separated and the aqueous layer extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave the alcohol in a high state of purity. In this way were prepared: 1-1′-naphthylethanol (92%; m. p. 66°) (cf. Lund, *Ber.*, 1937, **70**, 1520); 1-1′-naphthylpropan-1-ol (77%; b. p. 168°/11 mm., n_D^{20} 1·6099) (cf. Levina, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 913); 1-1′-*naphthylbutan*-1-*ol* (80%; b. p. 198°/19 mm., n_D^{20} 1·6042) (Found: C, 84·0; H, 8·1. $C_{14}H_{16}O$ requires C, 84·0; H, 8·1%) [3 : 5-*dinitrobenzoate*, m. p. 129—130° (from ether) (Found: C, 63·8; H, 4·4; N, 7·1. $C_{21}H_{18}O_6N_2$ requires C, 63·9; H, 4·6; N, 7·1%)]; and 1-1′-*naphthylpentan*-1-*ol* (80%; m. p. 65—66°) (Found: C, 84·1; H, 8·2. $C_{15}H_{18}O$ requires C, 84·1; H, 8·2%) [3 : 5-*dinitrobenzoate*, m. p. 96—97° (from alcohol) (Found: C, 64·8; H, 4·8; N, 6·9. $C_{22}H_{20}O_6N_2$ requires C, 64·7; H, 4·9; N, 6·9%)].

Preparation of α-*Alkyl*-1-*naphthylmethyl Bromides.*—1-Bromo-1-1′-naphthylethane was prepared from the corresponding alcohol by the method of Bachmann and Edgerton (*loc. cit.*). Similarly were prepared 1-*bromo*-1-1′-*naphthylpropane* (78%; m. p. 38—39°) (Found: C, 62·8; H, 5·4; Br, 32·0. $C_{13}H_{13}Br$ requires C, 62·6; H, 5·4; Br, 32·1%), 1-bromo-1-1′-naphthylbutane (79%; b. p. 134°/2 mm.) (decomposes on storage), and 1-bromo-1-1′-naphthylpentane (80%; b. p. 122/4 mm.) (decomposes on storage).

Preparation of β-*Alkyl*-β-1-*naphthylpropionic Acids.*—β-1-Naphthylbutyric acid was prepared by the method of Bachmann and Edgerton (*loc. cit.*). Similarly were prepared β-1-*naphthylvaleric acid* [75%; m. p. 70—70·5° (from light petroleum)] (Found: C, 78·9; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%), 3-1′-*naphthylhexanoic acid* [88·2%; m. p. 64—65° (from light petroleum–benzene)] (Found: C, 79·3; H, 7·3. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%), and 3-1′-*naphthylheptanoic acid* [73%; b. p. 188—190°/2 mm., m. p. 35—36° (Found: C, 79·7; H, 7·9. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%)]. The intermediate malonic esters were not purified.

Cyclisation of β-1-*Naphthylbutyric Acid.*—A solution of this acid (20 g.) in anhydrous hydrogen fluoride (100 g.) was kept for 24 hr. at room temperature, then poured on ice and extracted with ether. After being washed with water and 5% sodium hydrogen carbonate solution and dried (Na_2SO_4) the ethereal extract was evaporated to a yellow-brown solid (17·1 g.). The

latter was dissolved in light petroleum and chromatographed through alumina (5 × 60 cm.). Elution was carried out with light petroleum. The first fractions yielded 3-methylperinaphthan-1-one (14·9 g.), m. p. 61—61·5°. Crystallisation from light petroleum gave colourless prisms, m. p. 61·5—62° (oxime, m. p. 129—130°). Lock and Gergely (*loc. cit.*) record m. p.s 62° and 130°. The 2 : 4-*dinitrophenylhydrazone* had m. p. 229—230° (Found : C, 63·9; H, 4·4; N, 14·8. $C_{20}H_{16}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%). The second series of fractions from the chromatography yielded 3-*methyl*-4 : 5-*benzindan*-1-*one* (1·0 g.), m. p. 40—43°. Crystallisation from light petroleum at −10° gave colourless crystals, m. p. 48—48·5° (Found : C, 85·7; H, 6·1. $C_{14}H_{12}O$ requires C, 85·7; H, 6·2%) [2 : 4-*dinitrophenylhydrazone*, m. p. 280—282° (Found : C, 63·7; H, 4·4; N, 14·8. $C_{20}H_{16}O_4N_4$ requires C, 63·8; H, 4·3; N, 14·9%)]. Final elution with benzene gave 3-methylperinaphthen-1-one (0·03 g.), m. p. 150—154°. Crystallisation from benzene yielded bright yellow crystals, m. p. 156—157° (Found : C, 86·5; H, 5·1. Calc. for $C_{14}H_{10}O$: C, 86·6; H, 5·2%). Criegee, Kraft, and Rank (*loc. cit.*) record m. p. 156°.

Dehydrogenation of 3-*Methylperinaphthan*-1-*one*.—A mixture of this ketone (0·5 g.) and anhydrous aluminium chloride in nitrobenzene (10 c.c.) was heated on a water-bath for 1 hr., then poured into water (100 c.c.), and ether (100 c.c.) was added. After filtering, the ethereal layer was separated and the aqueous layer extracted with ether. The residue obtained on evaporation, under reduced pressure, of the dried (Na_2SO_4) combined extracts, was dissolved in light petroleum and chromatographed (alumina). Elution with light petroleum–ether (4 : 1) gave 3-methylperinaphthen-1-one (0·1 g.), m. p. 156—157° after recrystallisation.

Cyclisation of β-1-*Naphthylvaleric Acid*.—This acid (20 g.) was cyclised as in the preceding case, to yield a yellow oil (12·5 g.). Chromatography in light petroleum through alumina (5 × 60 cm.) and elution with light petroleum gave 3-*ethylperinaphthan*-1-*one* (8·2 g.) as a viscous yellow liquid, b. p. 126/2 mm. (Found : C, 86·0; H, 6·6. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%) [2 : 4-*dinitrophenylhydrazone* (scarlet crystals from benzene), m. p. 183—184° (Found : C, 64·5; H, 4·7; N, 14·1. $C_{21}H_{18}O_4N_4$ requires C, 64·6; H, 4·6; N, 14·3%)]. Further elution with light petroleum yielded 3-*ethyl*-4 : 5-*benzindan*-1-*one* (3·8 g.), m. p. 44—45° after recrystallisation from light petroleum (Found : C, 85·9; H, 6·7. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%) [2 : 4-*dinitrophenylhydrazone* (scarlet crystals from glacial acetic acid), m. p. 248—249° (Found : C, 64·5; H, 4·7; N, 14·1. $C_{21}H_{18}O_4N_4$ requires C, 64·6; H, 4·6; N, 14·3%)]. Final elution with light petroleum–benzene (1 : 1) gave 3-*ethylperinaphthen*-1-*one* (3·7 mg.), m. p. 90°. Crystallisation from light petroleum–benzene yielded yellow crystals, m. p. 94—95° (Found : C, 86·6; H, 6·2. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%).

Dehydrogenation of 3-*Ethylperinaphthan*-1-*one*.—This ketone (0·5 g.) was dehydrogenated, as for the 3-methyl analogue, to 3-ethylperinaphthen-1-one (0·2 g.).

Cyclisation of 3-1′-*Naphthylhexanoic Acid*.—(*A*) This acid (20 g.) was cyclised as in the previous case, to a pale yellow oil (17·0 g.). Chromatography in light petroleum through alumina (5 × 60 cm.) and elution with light petroleum–benzene (9 : 1) gave 3-n-*propylperinaphthan*-1-*one* (5·2 g.) (b. p. 154—156°/2 mm.) which at 0° yielded pale yellow crystals, m. p. 21—22° (Found : C, 85·7; H, 7·1. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%) [2 : 4-*dinitrophenylhydrazone*, m. p. 201—202° (scarlet crystals from acetic acid) (Found : C, 65·4; H, 5·0; N, 13·9. $C_{22}H_{20}O_4N_4$ requires C, 65·3; H, 5·0; N, 13·8%)]. Further elution gave a yellow solid, m. p. 58—68°, which on fractional crystallisation from light petroleum gave 3-n-*propyl*-4 : 5-*benzindan*-1-*one* (3·0 g.), m. p. 69·5—70° (Found : C, 85·7; H, 5·1. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%) [2 : 4-*dinitrophenylhydrazone*, m. p. 259—260° (scarlet crystals from acetic acid) (Found : C, 65·4; H, 5·0; N, 13·8. $C_{22}H_{20}O_4N_4$ requires C, 65·3; H, 5·0; N, 13·8%)], and 3-n-*propylperinaphthen*-1-*one* (0·9 g.), m. p. 84—85° (Found : C, 87·0; H, 6·1. $C_{16}H_{14}O$ requires C, 86·5; H, 6·3%). Final elution with ether gave a considerable amount of tar. (*B*) The cyclisation product (8·6 g.) was chromatographed in light petroleum through alumina (5 × 15 cm.) and eluted successively with light petroleum–ether mixtures in the ratio of 9 : 1, 8 : 2, 7 : 3, 6 : 4, and 5 : 5, to yield 3-*n*-propylperinaphthan-1-one (7·0 g.), 3-*n*-propyl-4 : 5-benzindan-1-one (1·4 g.), and 3-*n*-propylperinaphthen-1-one (0·02 g.).

Cyclisation of 3-1′-*Naphthylheptanoic Acid*.—This acid (20 g.) was cyclised as in the previous case, to yield a yellow oil (17·1 g.). Chromatography in light petroleum–ether (9 : 1) through alumina (5 × 15 cm.) and elution with the same solvent nixture gave 3-n-*butylperinaphthan*-1-*one* (14·0 g.), b. p. 178°/3·5 mm. (Found : C, 85·6; H, 7·5. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%) [2 : 4-*dinitrophenylhydrazone*, m. p. 212—214° (scarlet crystals from acetic acid) (Found : C, 66·0; H, 5·2; N, 13·0. $C_{23}H_{22}O_4N_4$ requires C, 66·0; H, 5·3; N, 13·4%)]. Further elution with light petroleum–ether (8 : 2) yielded 3-n-*butyl*-4 : 5-*benzindan*-1-*one* (2·8 g.), m. p. 29—30° after recrystallisation from light petroleum–benzene (9 : 1) at −20° (Found : C, 85·7; H, 7·7%)

[2 : 4-*dinitrophenylhydrazone*, m. p. 253—254° (scarlet crystals from acetic acid) (Found : C, 65·9; H, 5·3; N, 13·0. $C_{23}H_{22}O_4N_4$ requires C, 66·0; H, 5·3; N, 13·4%)]. Final elution with light petroleum–ether (1 : 1) gave 3-n-*butylperinaphthen*-1-*one* as pale yellow crystals, m. p. 82—84° after crystallisation from light petroleum–benzene (9 : 1) (Found : C, 86·5; H, 6·7. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

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Syntheses in the Piperidine Series. Part II. The Preparation of Piperidyl Ethers and Related Compounds.*

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The preparation of ethers from secondary alcohols and 4-fluoronitrobenzene by use of potassium *tert.*-butoxide is described.

THE object of this work was to prepare various ethers, containing basic nitrogenous groups, for evaluation as anti-tubercular compounds.

In Part I * methods of synthesising piperidin-4-ol and related compounds, required for this work, were described. Another route to piperidin-4-ol has been investigated, involving hydrolysis of 4-pyridylpyridinium dichloride (Koenigs and Greiner, *Ber.*, 1931, **64**, 1052) to 4-hydroxypyridine, followed by hydrogenation. Contrary to the findings of these workers, the crude pyridylpyridinium dichloride was found to be unsatisfactory as starting material for hydrolysis and the recommended purification of it, involving evaporation at ordinary pressure, led to decomposition. Purification of 4-pyridylpyridinium dichloride employing evaporation under reduced pressure gives a satisfactory product which may be hydrolysed to 4-hydroxypyridine in excellent yields, without the aid of an autoclave. This is achieved by working with concentrated aqueous solutions and thereby raising the boiling point.

Hydrogenation of 4-hydroxypyridine in absolute alcohol, in presence of Raney nickel, did not proceed below 200°/100 atm., under which conditions the product was essentially 1-ethylpiperidin-4-ol, formed by interaction with the solvent. Use of Adams catalyst did not lead to hydrogenation. When water was used as a solvent the hydrogenation gave the required piperidin-4-ol, but only in poor yields. As some of the secondary alcohols, from which the required ethers were to be prepared, were difficult to obtain in quantity, a method of preparing ethers from secondary alcohols was needed which did not require an excess of the alcohol.

*cyclo*Hexyl *p*-nitrophenyl ether may be readily prepared from 4-fluoronitrobenzene and the potassium salt of *cyclo*hexanol, with *cyclo*hexanol as a solvent, but if benzene is used as a solvent no ether is formed. Although Whalley (*J.*, 1950, 2241) found that 1-fluoro-2 : 4-dinitrobenzene reacts with primary, secondary, and tertiary alcohols in benzene in the presence of triethylamine, no similar reaction took place between 4-fluoronitrobenzene and *cyclo*hexanol in the presence of triethylamine when benzene, chlorobenzene, or *cyclo*hexanol was used as solvent.

Eventually, it was found that ethers could be prepared from equimolecular proportions of *p*-fluoronitrobenzene and a secondary alcohol in the presence of potassium *tert.*-butoxide in *tert.*-butanol, indicating that the equilibrium

$$Me_3C{\cdot}O^- + {>}CH{\cdot}OH \rightleftharpoons Me_3C{\cdot}OH + {>}CH{\cdot}O^-$$

lies so far to the right that it may be utilised for preparative purposes. In the absence of *cyclo*hexanol, *p-tert.*-butoxynitrobenzene was formed.

Both *cyclo*hexyl and *tert.*-butyl *p*-nitrophenyl ether were reduced to the corresponding amino-ethers and these yielded stable acetyl derivatives. Similarly, *p*-acetamidophenyl

* Part I, *J.*, 1952, 1164.

1-methyl- and 1-acetyl-4-piperidyl ether were prepared from 1-methyl- and 1-acetylpiperidin-4-ol respectively.

If *p*-fluoronitrobenzene is replaced by 4-chloropyridine, pyridyl ethers are formed by this method, *e.g.*, *cyclo*hexyl 4-pyridyl ether. This compound gave a picrate but attempts to obtain a hydrochloride or methiodide from it yielded oils. *n*-Alkyl 4-pyridyl ethers normally give solid salts (Koenigs and Neumann, *Ber.*, 1915, **48**, 959; Renshaw and Conn, *J. Amer. Chem. Soc.*, 1937, **59**, 297), and the possibility that this substance might be 1-*cyclo*hexyloxypyrid-4-one was examined. According to Haitinger and Lieben (*Monatsh.*, 1885, **6**, 317), 4-methoxypyridine readily undergoes fission on treatment with hydriodic acid, whilst the isomeric 1-methylpyrid-4-one remains unchanged. The product formed from 4-chloropyridine and *cyclo*hexanol gave *cyclo*hexyl iodide and 4-hydroxypyridine, indicating that it was the *cyclo*hexyl ether.

Experimental

4-Pyridylpyridinium Dichloride.—The following procedure gave the best yield. Dry pyridine (200 g.) was gradually added to thionyl chloride (600 g.), cooled below 20°, and the whole set aside for 3 days at room temperature. Volatile materials were then removed at the water-pump, leaving a dark-brown crystalline mass. This was triturated with absolute alcohol (250 c.c.) at 0°, filtered off, washed with cold absolute alcohol (2 × 200 c.c.), and dried in vacuum. The crude product (183 g.) was dissolved in water (100 c.c.) and 2N-hydrochloric acid (300 g.), animal charcoal (10 g.) was added, and the mixture boiled for 5 min. After hot filtration, the filtrates were again treated with charcoal (10 g.), to give a light-orange solution which was evaporated at the water-pump to 200 c.c. Absolute alcohol (400 c.c.) was added and the mixture cooled to 0°. The product was filtered off, washed with absolute alcohol (200 c.c.), and dried in vacuum. The pale yellow crystals (167 g.) melted at 158—160°, softening between 153° and 158°. Recrystallisation from methanol (30 c.c.) gave material (113 g.), m. p. 158—160°. Concentration of the mother-liquor gave a further crop (25 g.) with the same m. p.

4-Hydroxypyridine.—Water was distilled from a solution of 4-pyridylpyridinium dichloride (120 g.) in water (54 c.c.) until the temperature of the mixture reached 130°. The solution was then refluxed for 24 hr. Water (150 c.c.) was added, followed by anhydrous sodium carbonate (75 g.), and the mixture was evaporated to dryness under reduced pressure. The resulting solid was extracted with absolute alcohol (3 × 100 c.c.), and the filtrates were treated with charcoal and then evaporated to a pale-yellow solid which was dried (P_2O_5). The yield of 4-hydroxypyridine (m. p. 120—130°) was 48 g. The nitrate, crystallised from 2N-nitric acid, melted at 204—205° (decomp.) (Found: C, 38·0; H, 3·8; N, 17·7. Calc. for $C_5H_6O_4N_2$: C, 38·0; H, 3·8; N, 17·7%). Bishop, Cavell, and Chapman (*J.*, 1952, 437) record m. p. 189—191°.

Catalytic Reductions of 4-Hydroxypyridine.—(*a*) 4-Hydroxypyridine (9·5 g.) in absolute alcohol (200 c.c.) with Raney nickel (1 g.) were hydrogenated at 200°/100 atm. Distillation, after removal of the catalyst, gave a viscous oil (7 g.), b. p. 98—102°/13 mm., which appeared to be 1-ethylpiperidin-4-ol (Emmert, D.-R.P. 292,871).

(*b*) 4-Hydroxypyridine (9·5 g.) in water (200 c.c.) with Raney nickel (1 g.) was hydrogenated at 170°/65 atm. The product was filtered, 2N-hydrochloric acid (75 c.c.) added, and the solution evaporated to dryness under reduced pressure. The resulting solid was dissolved in absolute alcohol (50 c.c.), filtered, and evaporated to dryness under reduced pressure. The solid was taken up in methanol (30 c.c.), and a solution of sodium methoxide [from sodium (2·3 g.) and methanol (30 c.c.)] was added. Sodium chloride was filtered off and the filtrates concentrated under reduced pressure to yield an oil which was distilled, giving piperidin-4-ol, b. p. 110—112°/14 mm. (1·3 g.), characterised as its sulphate, m. p. 66—68°. Unchanged 4-hydroxypyridine (7·0 g.) remained in the distillation flask.

cyclo*Hexyl* p-*Nitrophenyl Ether.*—(*a*) Powdered potassium hydroxide (2 g.) was heated with *cyclo*hexanol (20 c.c.) on the steam-bath until a clear solution was obtained. This was allowed to cool a little and then *p*-fluoronitrobenzene (5 g.) was gradually added, with shaking. The mixture was heated on the steam-bath for 15 min., cooled, and poured into dilute hydrochloric acid. The insoluble material was isolated with ether, washed with dilute sodium hydroxide solution, dried (Na_2SO_4), and distilled, giving cyclo*hexyl* p-*nitrophenyl ether*, b. p. 189—191°/12 mm. (3·6 g.) (Found: C, 65·0; H, 6·9; N, 6·8. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%).

(*b*) Potassium (1·1 g.) and *cyclo*hexanol (20 c.c.) were heated together on the steam-bath until they had reacted. The mixture was allowed to cool, *p*-fluoronitrobenzene (5 g.) was added in

one portion, and the mixture was heated on the steam-bath for 15 min. The product was isolated by pouring the mixture into water, extracting with benzene, washing the benzene layer with alkali, drying the benzene layer (Na_2SO_4), and finally distilling it, to give *cyclo*hexyl *p*-nitrophenyl ether, b. p. 147—148°/0·3 mm. (4·5 g.).

(*c*) Potassium (1·95 g.), *cyclo*hexanol (6 g.), and anhydrous benzene (50 c.c.) were heated under reflux until all the potassium had reacted. The benzene was removed under reduced pressure and *tert.*-butanol (25 c.c.) was added. The mixture was boiled on the water-bath under reflux for 10 min. after the last of the solid had dissolved and then cooled to 30° at which temperature *p*-fluoronitrobenzene (7 g.) was added in one portion. The temperature was held at 40° by cooling and, after the exothermic reaction had diminished, the mixture was heated on the steam-bath for 15 min. Excess of *tert.*-butanol was removed under reduced pressure and the residue was extracted with hot benzene (50 c.c.). The benzene solution was distilled, giving *cyclo*hexyl *p*-nitrophenyl ether, b. p. 145—147°/0·3 mm. (5·9 g.).

p-*Aminophenyl* cyclo*Hexyl Ether.*—(*a*) *cyclo*Hexyl *p*-nitrophenyl ether (3·6 g.) in 95% aqueous alcohol (20 c.c.) was stirred under reflux on the steam-bath with iron powder (8·2 g.) and concentrated hydrochloric acid (2 c.c.) for 3 hr. 95% Alcohol (30 c.c.) was then added and the mixture was allowed to cool. After neutralisation with concentrated aqueous ammonia, the mixture was centrifuged and the alcoholic solution concentrated under reduced pressure to give a semi-crystalline mass. This was dissolved in water (40 c.c.) and 2N-hydrochloric acid (20 c.c.), and the mixture was extracted with ether. The aqueous portion was made alkaline with 2N-sodium hydroxide, and the resulting oil extracted with ether, dried (Na_2SO_4), and distilled to give a colourless oil, b. p. 128°/0·2 mm. (2·1 g.).

(*b*) The amino-ether was also obtained by hydrogenation of *cyclo*hexyl *p*-nitrophenyl ether (9·8 g.) in absolute alcohol (80 c.c.) in the presence of Raney nickel at 60° and at atmospheric pressure. The yield was 6 g., b. p. 113—114°/0·004 mm. The *acetyl* derivative, crystallised from absolute alcohol, had m. p. 155° (Found : C, 72·4; H, 8·1; N, 6·05. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·2; N, 6·0%).

tert.-*Butyl* p-*Nitrophenyl Ether.*—The ether, prepared from *tert.*-butanol (20 c.c.), potassium (1·4 g.), and *p*-fluoronitrobenzene (5 g.) by the above method, had b. p. 97°/0·2 mm. (4·3 g.) and a powerful odour.

p-*Aminophenyl* tert.-*Butyl Ether.*—Reduction of the nitro-ether (5 g.) as in (*a*) above gave the amino-ether (2·7 g.), b. p. 91—92·5°/0·4 mm., m. p. 73—74° [from light petroleum (b. p. 60—80°)]. The *acetyl* derivative crystallised from 66% aqueous alcohol as plates, m. p. 130° (Found : C, 69·8; H, 8·4; N, 6·95. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3; N, 6·8%).

1-*Methyl*-4-*piperidyl* p-*Nitrophenyl Ether.*—A mixture of 1-methylpiperidin-4-ol (13·5 g.), *tert.*-butanol (75 c.c.), and potassium (3·4 g.) was heated under reflux until all the potassium had reacted. *p*-Fluoronitrobenzene (15·5 g.) was added in one portion at 30°. The mixture was shaken and the temperature was allowed to rise to 40°. When the exothermic reaction had abated the mixture was heated on the steam-bath for 15 min. The *tert.*-butanol was removed under reduced pressure and the residue was extracted with boiling benzene (100 c.c.), from which, on concentration under reduced pressure, orange crystals were deposited (23 g.). These were boiled with light petroleum (b. p. 60—80°; 150 c.c.), and the decanted solution gave orange-yellow plates, m. p. 96—98° (16 g.). The *ether* was finally crystallised from *iso*propyl ether, giving pale yellow crystals, m. p. 100—101° (Found : C, 61·1; H, 6·7; N, 11·9. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%). The *picrate* crystallised from 75% aqueous acetone as yellow needles, m. p. 204—205° (Found : C, 46·9; H, 3·8; N, 14·7. $C_{18}H_{19}O_{10}N_5$ requires C, 46·5; H, 4·1; N, 15·0%). The *methiodide* crystallised from 95% aqueous alcohol as pale yellow needles, m. p. 265—266° (Found : C, 41·0; H, 4·9; N, 7·5. $C_{13}H_{19}O_3N_2I$ requires C, 41·3; H, 5·1; N, 7·4%).

p-*Aminophenyl* 1-*Methyl*-4-*piperidyl Ether.*—The nitro-ether (9·4 g.) was hydrogenated in absolute alcohol (150 c.c.) in the presence of Raney nickel (4 g.) at 20°/5 atm. The catalyst was filtered off and the solvent removed under pressure to give a pale-brown oil which slowly crystallised. Difficulty was experienced in recrystallising this material, a small amount of crystals being obtained, m. p. 74—76°, from ether, but these appeared to be hygroscopic. The acetyl derivative crystallised from water as a hydrate, m. p. 107°, which was converted into an acetyl compound, m. p. 130°, on drying ($CaCl_2$). This compound reverted to that melting at 107° when kept in air. Both compounds gave the same *methiodide*, m. p. 226° (from methanol) (Found : C, 46·1; H, 5·9; N, 7·2; I, 32·7. $C_{15}H_{23}O_2N_2I$ requires C, 46·1; H, 5·9; N, 7·2; I, 32·5%).

1-*Acetyl*-4-*piperidyl* p-*Nitrophenyl Ether.*—To potassium *tert.*-butoxide prepared from potas-

sium (1 g.) and *tert.*-butanol (25 c.c.) was added 1-acetylpiperidin-4-ol (4 g.). The resulting solution was boiled for 15 min. and then cooled to 35°; then *p*-fluoronitrobenzene (4 g.) was added in one portion, with shaking. The temperature was held at 45° until the exothermic reaction had ceased and was finally raised to 80° and held at this temperature for 15 min. After removal of the *tert.*-butanol under reduced pressure, the *nitro-ether* was isolated by benzene-extraction, forming yellow crystals, m. p. 94—95° (3·8 g.), from diethylamine (Found: C, 58·9; H, 6·4; N, 10·8. $C_{13}H_{16}O_4N_2$ requires C, 59·1; H, 6·1; N, 10·6%).

1-*Acetyl*-4-*piperidyl* p-*Aminophenyl Ether*.—Hydrogenation of the nitro-ether (2·64 g.) in absolute alcohol (50 c.c.) in the presence of Raney nickel (1·0 g.) at 45°/1 atm. gave a pale brown oil (2·3 g.) which slowly crystallised. This was converted into the *acetyl* derivative (1·8 g.), m. p. 158° (from hot water) (Found: C, 65·3; H, 7·1; N, 10·4. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·3; N, 10·1%).

cyclo*Hexyl* 4-*Pyridyl Ether*.—(*a*) Potassium (1·3 g.) and *cyclo*hexanol (20 c.c.) were heated together until the reaction was complete. 4-Chloropyridine (3·8 g.) was added in one portion, and when the exothermic reaction had ceased, the mixture was boiled for 3 hr. Sodium chloride was deposited from the hot solution but redissolved on cooling. The product was isolated in the usual way with benzene, and distilled to give a colourless oil, b. p. 139—142°/10 mm. (5·1 g.). The substance was insoluble in water, but readily dissolved in dilute acids from which it could be regenerated. Dry hydrogen chloride in ether reacted with it, as did methyl iodide, to give an oil. With alcoholic picric acid a *picrate* was formed, m. p. 148° (from absolute alcohol) (Found: C, 50·3; H, 4·4; N, 14·0. $C_{17}H_{18}O_8N_4$ requires C, 50·3; H, 4·5; N, 13·8%). The base (2 g.), heated on the steam-bath for 3 hr. with concentrated hydriodic acid (15 g.), gave *cyclo*hexyl iodide (1·3 g.), b. p. 71°/14 mm., and 4-hydroxypyridine (1·2 g.) characterised as the nitrate, m. p. 204—205° (decomp.).

(*b*) Potassium (1·4 g.) and *tert.*-butanol (25 c.c.) were heated together until completion of the reaction, and *cyclo*hexanol (4 g.) was then added and the mixture boiled for 15 min. 4-Chloropyridine (4 g.) was added and the mixture heated in a sealed tube at 150° for 15 hr. The product was isolated in the usual manner, giving 4 g. of material identical with that obtained as in (*a*).

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Complex Fluorides. Part II. Studies on Fluoroferrates and on Hydrogen Bonding in Complex Fluorides.*

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There is at present no evidence for hydrogen bonding as an important factor in complex fluorides containing the ammonium ion. Infra-red spectroscopy shows no more than slight variation in the position of the 1400 cm.$^{-1}$ N–H vibration in such compounds, and more detailed work on the analytical composition and structures of the fluoroferrates appears to refute the hitherto accepted evidence for strong hydrogen bonding in ammonium fluoroferrate. In connection with this investigation an electrolytic method has been developed for the preparation of complex fluorides of manganese(IV).

In Part I * we drew attention to a possible connection between the Fe–F bond type in the FeF_6^{3-} ion (deduced from the magnetic properties to be "outer orbital" in character) and the evidence cited by Pauling ("Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, N.Y., 1940, p. 300) for strong hydrogen bonding in ammonium hexafluoroferrate (namely, the relative sizes of the cubic or pseudo-cubic unit cells of the alkali-metal and ammonium hexafluoroferrates). Lattice constants reported for these substances are: Li_3FeF_6, $a = 8·88$ (Minder, *Z. Krist.*, 1937, **96**, 15); $(NH_4)_3FeF_6$, $a = 9·17$ (*idem, ibid.*), 9·10 (Pauling, *J. Amer. Chem. Soc.*, 1924, **46**, 2738; Rice, Turner, and Brydon, *Nature*, 1952, **169**, 749; Steward and Rooksby, *Acta Cryst.*, 1953, **6**, 49); Na_3FeF_6, $a = 9·26$; K_3FeF_6, $a = 9·93$; Rb_3FeF_6, $a = 10·23$; Cs_3FeF_6, $a = 10·46$ Å (Minder, *loc. cit.*).

* Part I, *J.*, 1953, 1783.

A knowledge of the structure and magnetic properties of ammonium hexafluorocobaltate, $(NH_4)_3CoF_6$, would shed light on this problem, but attempts to make this substance by the method used by Mitchell (Thesis, Univ. Buffalo, 1940) for the preparation of the corresponding potassium salt have failed. This may be due to the extreme insolubility of the hydrated fluoride, $Co_2F_6,7H_2O$ (Barbieri and Calzolari, *Atti R. Accad. Lincei*, 1905, **14**, 464; *Z. anorg. Chem.*, 1928, **170**, 109), an intermediate product, compared with that of the desired ammonium salt. Although among complex chlorides and bromides the lattice dimensions of ammonium and rubidium salts of the same acid are almost identical, and their solubilities are of the same order of magnitude, yet among complex fluorides ammonium salts are invariably considerably more soluble than the corresponding potassium or rubidium salts. The solubilities (in g. per 100 g. of water) of potassium, ammonium, and rubidium fluoroborates, for example, are: KBF_4, 0·6[17] (de Boer and van Liempt, *Rec. Trav. chim.*, 1927, **46**, 124); $RbBF_4$, 0·6[17] (*idem, ibid.*); NH_4BF_4, 25[16] (Stolba, *Centr. Ges. chem. Grossind.*, 1890, **7**, 459). Those of the fluorosilicates (in the same units) are: K_2SiF_6, 0·132[16] (Carter, *Ind. Eng. Chem.*, 1930, **22**, 886); Rb_2SiF_6, 0·160[20] (Stolba, *J. pr. Chem.*, 1870, **103**, 396); $(NH_4)_2SiF_6$, 18·58[17·5] (*idem, Chem. Zentr.*, 1877, **8**, 418). For the fluorotitanates the values reported (in the same units) are: $(NH_4)_2TiF_6$, 25[20] (Ginsberg, *Z. anorg. Chem.*, 1932, **204**, 225); Rb_2TiF_6, 0·8[20] (*idem, ibid.*). Quantitative data for other complex fluorides are lacking, but similar relationships have been reported for the fluoroberyllates, -germanates, and -aluminates.

A probable explanation is that the differences in solubility arise from small differences in the lattice energies of the compounds. To a first approximation we may regard solubility as determined by the relative magnitudes of lattice energy and ionic solvation energies. Because of the exponential nature of the relation between an equilibrium constant (in this instance, a solubility product) and the corresponding change in free energy (in this instance, the lattice energy), solubility should be very much affected by even small changes in lattice energy. Accordingly, we have compared the molecular volumes (as determined from *X*-ray data) of potassium, ammonium, and rubidium salts of complex fluoro-acids having the same structure type with those of analogous complex chloro- and bromo-acids. The results are given in the following table.

Molecular volume, cm.^{3} × 10^{-24}

	$PdCl_6''$	$PdBr_6''$	$PtCl_6''$	$PtBr_6''$	$TeCl_6''$	$SeCl_6''$	$SnBr_6''$	$SnCl_6''$	$PbCl_6''$	SiF_6''
K^+	231·3 [4]	269·3 [4]	229·8 [3]	270·8 [4]	261·0 [3]	—	290·2 [3]	248·7 [3]	—	135·0 [7]
NH_4^+	239·0 [4]	276·5 [4]	238·0 [3]	279·8 [4]	263·8 [3]	245·0 [3]	297·0 [5]	253·7 [3]	260·3 [3]	148·0 [8, 1]
Rb^+	241·0 [4]	280·3 [4]	241·5 [3]	282·0 [4]	267·7 [3]	248·5 [3]	301·5 [5]	257·0 [3]	264·7 [3]	150·4 [7, 1]

	GeF_6''	TiF_6''	MnF_6''	BF_4'	SbF_6'	SbF_5''	Sb_4F_{13}'	BeF_4''	AlF_4'
K^+	127·3 [9]	130·2 [2, 11]	131·6 [12]	82·15 [13]	—	138·7 [16]	256·0 [17]	101·1 [18]	77·5 [6]
NH_4^+	141·3 [9]	147·9 [2]	144·1 [1]	92·35 [14]	131·5 [15]	153·3 [16]	263·8 [17]	114·7 [18]	81·6 [6]
Rb^+	140·5 [10]	143·5 [2]	140·7 [12]	91·85 [14]	132·0 [15]	149·9 [16]	263·6 [17]	113·2 [18]	81·8 [6]

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We find that, whereas in the case of salts of complex chloro- and bromo-acids the molecular volume of the ammonium salt lies between those of the potassium and rubidium salts, yet in all the reported examples of complex fluorides (except the hexafluorosilicates) the molecular volume of the ammonium salt is approximately equal to or greater than that of the rubidium salt. We have confirmed that the fluorosilicates do constitute an exception by redetermining their unit-cell sizes, and obtaining values $a = 8·39$ and $a = 8·44$ Å, respectively, for ammonium and rubidium fluorosilicates. These are in close agreement with those previously reported for the ammonium salt [$a = 8·34$ (Ketelaar, *Z. Krist.*, 1935, **92**, 155), 8·38 (Bozorth, *J. Amer. Chem. Soc.*, 1922, **44**, 1066)] and the rubidium salt [$a = 8·45$ Å (Ketelaar, *loc. cit.*)]. The correlation we suggest must, therefore, be regarded as probable but not proved.

As we failed to prepare ammonium hexafluorocobaltate, we studied the application of the electrolytic method to the preparation of complex fluorides of other transition metals in their higher oxidation states. By electrolytic oxidation of a suspension of manganous fluoride in aqueous hydrofluoric acid an oxidation state, in solution, of slightly greater than 3 was attained. When a saturated solution of potassium hydrogen difluoride in aqueous hydrofluoric acid was added to this solution and the electrolysis was continued, a deposit of yellow crystals of potassium hexafluoromanganate(IV) was obtained. A sample of the hitherto unknown ammonium hexafluoromanganate(IV) was obtained in the same manner but in smaller yield. *X*-Ray powder photography shows the potassium (hexagonal, $a = 5{\cdot}70$, $c = 9{\cdot}33$) and ammonium (hexagonal, $a = 5{\cdot}91$, $c = 9{\cdot}55$ Å) salts to be isomorphous. The values obtained for the potassium salt agree well with those reported by Bode and Wendt (*loc. cit.*) and tabulated in Part I (*loc. cit.*).

Complex salts of manganese(III) can be obtained by omitting the second stage of electrolysis and allowing crystallisation to take place. Electrolysis of a suspension of plumbous fluoride or nickel fluoride in aqueous hydrofluoric acid did not give a solution of higher oxidation state than 2.

Since we were unable to investigate the structure of ammonium hexafluorocobaltate we re-examined the structural chemistry of the fluoroferrates. In a recent paper by Steward and Rooksby (*loc. cit.*) values are given for the lattice constants of sodium, potassium, and ammonium hexafluoroaluminates. These values are widely different from Minder's values (*loc. cit.*) for the fluoroferrates, despite the similarity in the tervalent radii of iron and aluminium.

From the Na^+–Fe^{3+}–F^- system in aqueous solution we find that only one phase can be isolated, and that this phase is isomorphous with cryolite, the unit cell sizes being respectively $a = 5{\cdot}51$, $b = 5{\cdot}74$, $c = 7{\cdot}94$, β approx. 90°, and $a = 5{\cdot}46$, $b = 5{\cdot}61$, $c = 7{\cdot}80$ Å, $\beta = 90°\ 10'$ (Naray-Szabo and Sasvari, *Z. Krist.*, 1938, **99**, 27). Analysis, however, establishes that the composition of this phase corresponds closely to $Na_{2{\cdot}0}FeF_{5{\cdot}0},1{\cdot}0H_2O$; the conclusion that "sodium hexafluoroferrate" does not have an analytical composition corresponding to Na_3FeF_6 was reached much earlier by Nicklès (*Rev. Scient.*, 1868, **5**, 391), Welo (*Phil. Mag.*, 1928, **6**, 496), and Röder ("Uber kristallisierte wasserfreie Fluor Verbindungen," Göttingen, 1863), but their conclusions appear to have been ignored by most later workers on the fluoroferrates, Minder included. It should be noted that natural and synthetic cryolite also show departures from the ideal composition Na_3AlF_6 (Tananaev and Lel'chuk, *Doklady Akad. Nauk S.S.S.R.*, 1943, **41**, 118).

In the system NH_4^+–Fe^{3+}–F^-, the only product obtained when the concentration ratio $NH_4^+ : Fe^{3+}$ exceeds **3 : 1** is a cubic phase with $a = 9{\cdot}10$ Å; this phase can be recrystallised from very dilute hydrofluoric acid without change, and its composition corresponds approximately to $(NH_4)_{2{\cdot}6}FeF_{5{\cdot}6},0{\cdot}4H_2O$. Since our value for the unit-cell size agrees well with all earlier determinations (for none of which chemical analyses are given) it seems impossible to avoid the conclusion that earlier investigations have been made, not on $(NH_4)_3FeF_6$, but on products of composition similar to that described above. The sample of the isomorphous ammonium fluoroaluminate investigated by Menzer (*Z. Krist.*, 1930, **73**, 113) had an analytical composition agreeing well with that calculated for $(NH_4)_3AlF_6$; however, Baud (*Compt. rend.*, 1902, **135**, 1337) has reported the formation of a compound with the $NH_4F : AlF_3$ ratio less than **3 : 1**.

We have been unable to identify a phase K_3FeF_6 among the products obtained by varying the K^+:Fe^{3+} ratio in the solutions used, and none of the powder photographs of our preparations has shown lines corresponding to the cubic phase reported by Minder (*loc. cit.*). With low potassium concentrations the product was found to be cubic ($a = 8{\cdot}21$ Å) and corresponded to $K_{1{\cdot}8}FeF_{4{\cdot}8},1{\cdot}5H_2O$. A non-cubic phase of approximate composition $K_2FeF_5,0{\cdot}5H_2O$ was obtained from solutions of higher potassium concentration. Attempts to interpret the *X*-ray powder pattern of this phase by analogy with Tl_2AlF_5 and K_2AlF_5,H_2O (Brosset, *Z. anorg. Chem.*, 1937, **235**, 139; "Electrokemisk och rontgenkristallographisk undersökning av complexa aluminiumfluorider," Stockholm, 1942) were not successful.

Comparison of cell dimensions for these compounds does not confirm the hitherto

accepted sequence for the lattice constants among the fluoroferrates, but it does show the order of difference to be expected from the conventional ionic radii of Na^+, K^+, and NH_4^+. The unit-cell sizes thus afford no evidence for the presence of strong hydrogen bonds in the fluoroferrates.

We therefore sought independent evidence of the presence or absence of hydrogen bonds by investigating the infra-red spectra of a large number of ammonium salts. The position of the N–H vibration at about 1400 $cm.^{-1}$ has been used as diagnostic of the presence of hydrogen bonding in ammonium fluoride (Bovey, *J. Chem. Physics*, 1950, **18**, 684); the frequency of this vibration is 1397 $cm.^{-1}$ in ammonium iodide, 1407 $cm.^{-1}$ in ammonium bromide, 1397 $cm.^{-1}$ in the chloride, and 1484 $cm.^{-1}$ in the fluoride. (We should mention, however, that in ammonium hydrogen difluoride the frequency is 1406 $cm.^{-1}$.) Among a wide range of ammonium oxy-salts (Miller and Wilkins, *Ind. Eng. Chem. Anal.*, 1952, **24**, 1253) and ammonium salts of chloro- and fluoro-complex acids the values for this N–H vibration frequency lie in the range 1390—1420 $cm.^{-1}$. Only in the fluoroberyllate (1426 $cm.^{-1}$), fluoroferrate and fluoroaluminate (1428 $cm.^{-1}$), and fluoroborate (1430 $cm.^{-1}$) is the frequency outside this range and is then only just so. Furthermore, in the fluoroborate the hydrogen bonding is insufficiently strong to affect the B–F vibration frequency, which is identical with that in the other alkali-metal fluoroborates (Coté and Thompson, *Proc. Roy. Soc.*, 1951, *A*, **210**, 217). We therefore conclude that there is no evidence for hydrogen bonding's being an important factor in the determination of the structure of any complex fluoride so far investigated.

Finally, it is of interest to consider what effect hydrogen bonding has on the interionic distance in ammonium fluoride, which, unlike the other halides, crystallises with the wurtzite structure. From the ionic radii of the fluoride and ammonium ions (1·33 and 1·48 Å, respectively) derived from halides having the sodium chloride type structure, the equilibrium interionic distance in the hypothetical sodium chloride type modification of ammonium fluoride should be 2·81 Å. From Madelung's constants for the sodium chloride ($A_{r_0} = 1{\cdot}7476$) and wurtzite ($A_{r_0} = 1{\cdot}641$) structures, the Born exponents being assumed to be the same in each case, r_0 for the wurtzite form of ammonium fluoride, no allowance being made for hydrogen bonding, should be $2{\cdot}81 \times 1{\cdot}641/1{\cdot}748 = 2{\cdot}64$ Å. An alternative calculation, based on Pauling's method (*op. cit.*, pp. 354, 367), leads to a value of 2·70 Å. The observed distance is 2·66 Å (Zachariasen, *Z. physikal. Chem.*, 1927, **127**, 218). In view of evidence from the unusual co-ordination number and infra-red spectrum in favour of the presence of strong hydrogen bonding, we can only conclude that interionic distance (as distinct from unusually close approach of non-bonded atoms) is unlikely to have any diagnostic value in this connection.

Experimental

Cobalt(III).—A saturated solution of cobaltous fluoride in 40% aqueous hydrofluoric acid was electrolysed at a potential of 2—3 v, the resistance of the cell being such that a current of 0·5—0·75 A was maintained. After 1—2 hours' electrolysis the blue hydrated fluoride, $Co_2F_6,7H_2O$, was deposited; this was filtered off by use of a pump, and washed first with a little 40% aqueous hydrofluoric acid, then immediately with several portions of absolute alcohol, and finally with dry ether. The solid was immediately transferred to a platinum crucible and stored in a vacuum-desiccator. After the initial drying period was passed, the solid could be stored almost indefinitely in a desiccator without decomposition. The hydrated fluoride was analysed for tervalent cobalt by adding a weighed quantity slowly, with vigorous stirring, to acidified potassium iodide solution. The iodine liberated was determined with thiosulphate (Found: Co, 32·8. Calc. for $Co_2F_6,7H_2O$: Co, 32·9%).

Ammonium hydrogen difluoride was added to the hydrated fluoride, before this was filtered off, either as the solid or as a saturated solution in aqueous hydrofluoric acid, and the electrolysis was continued. No evidence was obtained for complex formation having taken place, and when solid ammonium hydrogen difluoride had been added the product appeared to be a mixture of the hydrated fluoride with undissolved ammonium hydrogen difluoride.

Manganese(IV).—Manganous carbonate was added to 40% aqueous hydrofluoric acid until a white suspension of manganous fluoride was obtained; this was electrolysed with a potential of 2—3 v and a current of about 0·75 A until a clear red-brown solution containing manganese(III) was obtained. Solid potassium hydrogen difluoride or a saturated solution of this in 40%

aqueous hydrofluoric acid was added to the liquid and the electrolysis was continued. Any deposit of crystals of manganese(III) complexes, formed on the addition of the alkali-metal salt, dissolved on further electrolysis, and was replaced by yellow crystals of the hexafluoromanganate(IV). The liquid was decanted from these crystals and they were washed first with a little 40% hydrofluoric acid and then with alcohol and ether; they were stored in a desiccator.

The *ammonium* salt was prepared in an analogous manner; owing to its greater solubility, however, the initial washing with hydrofluoric acid was omitted [Found, for K_2MnF_6: Mn, 21·95. Calc.: Mn, 22·25. Found, for $(NH_4)_2MnF_6$: Mn, 26·4. $(NH_4)_2MnF_6$ requires Mn, 26·8%].

Manganese(III).—The oxidation state of the solution obtained by the electrolysis of a suspension of manganous fluoride in 40% aqueous hydrofluoric acid was determined by commencing with a weighed quantity of manganous carbonate, and determining the iodine liberated when the resulting solution containing manganese(III) was added to acidified potassium iodide. Several such estimations all gave values slightly higher than 3, with a mean of 3·06, for the oxidation state of the manganese. Red-brown crystals of manganese(III) complexes were obtained by adding excess of a saturated solution of potassium hydrogen difluoride in hydrofluoric acid to this solution. The supernatant liquid having been drained off, the crystals were washed with acetone and ether. Their *X*-ray powder photograph did not resemble that given by a sample of the salt K_2MnF_5,H_2O prepared by Müller and Koppe's method (*Z. anorg. Chem.*, 1910, **68**, 160), although many of the lines did occur on both, suggesting that the product was a mixture. After a sample of these crystals had been washed carefully with a saturated solution of potassium hydrogen difluoride in aqueous hydrofluoric acid, a pink residue resembling the K_2MnF_5,H_2O preparation and giving an identical *X*-ray powder pattern was obtained.

Lead(IV).—Use of the simple electrolytic cell employed for the manganese and cobalt preparations resulted in deposition of lead on the cathode when a suspension of plumbous fluoride in aqueous hydrofluoric acid was electrolysed. On use of a cell in which the anode compartment was connected to the cathode compartment by a bridge consisting of a rolled filter-paper soaked in hydrofluoric acid, and electrolysis at a potential of 30—40 v with a current of 0·24 A, owing to the high resistance of the cell, the solution remaining did not liberate iodine from acidified potassium iodide and contained only a very small quantity of lead in solution. The only evidence for any oxidation's having taken place after the current had been passed for several hours was a brown stain of PbO_2 above the liquid level in the anode compartment.

Nickel(IV).—Electrolysis of a solution of nickel(II) fluoride in 40% aqueous hydrofluoric acid gave no evidence of oxidation after several hours.

Iron(III).—Fluoroferrates were prepared by mixing a saturated solution of the alkali-metal fluoride, or ammonium fluoride, in aqueous hydrofluoric acid with a solution of either ferric chloride or ferric hydroxide in hydrofluoric acid. The molecular proportions in which these were present were varied in an attempt to obtain different phases in the product.

Sodium fluoroferrate was the only product obtained from sodium fluoride and ferric hydroxide solutions over the whole range of Na–Fe concentrations up to the point where considerable quantities of sodium hydrogen difluoride were co-precipitated. Analysis were consistent with a formula of Na_2FeF_5,H_2O for the sodium fluoroferrate. The presence of water in the compound was confirmed by infra-red spectroscopy (Found: Fe, 26·1; F, 44·5. Calc. for Na_2FeF_5,H_2O: Fe, 26·0; F, 44·1%).

With NH_4 : Fe ratios greater than 3 : 1 a white precipitate was formed immediately; the *X*-ray powder diagram was the same in all cases, but the products showed a slight variation about a mean composition $(NH_4)_{2\cdot6}FeF_{5\cdot6},0{\cdot}4H_2O$ [Found, in a typical preparation: NH_4, 23·3; Fe, 26·2; F, 48·7. Calc. for $(NH_4)_{2\cdot6}FeF_{5\cdot6},0{\cdot}4H_2O$: NH_4, 21·9; Fe, 26·2; F, 49·7%]. When the NH_4 : Fe ratio was less than 3 : 1 no precipitate was formed on mixing of the solutions, and when the bulk of the solution was reduced a crop of pale green crystals was obtained. Analysis showed this to have consisted almost entirely of ferric fluoride.

For the potassium salt, when the K : Fe ratio was 3—4 : 1 the product was a cubic phase which corresponded approximately to K_2FeF_5,H_2O. With higher concentrations of potassium, however, the water content of the product diminished, and a non-cubic phase corresponding approximately to K_2FeF_5 was obtained. Throughout the series of preparations *X*-ray powder photography failed to reveal the existence of any cubic phase corresponding either to Minder's reported value for K_3FeF_6 or to a cell size which might be expected for K_3FeF_6 from the values obtained for the sodium and ammonium salts (Found: K, 29·2; Fe, 22·7; F, 36·7. Calc. for K_2FeF_5,H_2O: K, 31·6; Fe, 22·7; F, 38·5. Found: K, 33·8; Fe, 24·8; F, 37·2. Calc. for K_2FeF_5: K, 34·0; Fe, 24·4; F, 41·4%).

Analytical Methods.—Potassium was determined gravimetrically as chloroplatinate, and ammonium ion by distillation from alkali into saturated boric acid solution, followed by titration with standard hydrochloric acid. Iron was determined gravimetrically as ferric oxide, fluorine as calcium fluoride (Grant, " Clowes and Coleman's Quantitative Chemical Analysis," Churchill, London, 15th Edn., 1944, p. 101). Methods used for the determination of cobalt(III), manganese(III), and manganese(IV) are described above. The presence of water as distinct from OH groups in the compounds was confirmed by infra-red spectroscopy.

Infra-red Spectroscopy.—The infra-red spectra of the ammonium salts were measured in suspension in Nujol and hexachlorobutadiene on a Perkin–Elmer Model 21 Spectrometer with rock-salt optics. The frequencies (in cm.$^{-1}$) of the N–H vibrations are tabulated below.

$(NH_4)_2SiF_6$	1405	—	—	3060	3150	—
$(NH_4)_2TiF_6$	1408	—	2870	—	—	3280
$(NH_4)_2GeF_6$	1408	—	2870	—	—	3280
$(NH_4)_2BeF_4$	1426	—	2925	—	3125	—
$(NH_4)_3CrF_6$	1418	—	2870	3030	—	3240
$(NH_4)_{2\cdot5}FeF_{5\cdot5},0{\cdot}4H_2O$	1428	—	2880	—	—	3250
$(NH_4)_3AlF_6$	1428	—	—	3060	—	3250
NH_4BF_4	1430	—	2930	—	—	—
$(NH_4)_2PbCl_6$	1408	—	—	—	—	3225
$(NH_4)_2PtCl_6$	1406	2770	2925	—	—	3221
$(NH_4)_2PtBr_6$	1403	—	2860	3050	3150	—
$(NH_4)_2SnCl_6$	1407	—	—	—	—	3220
NH_4HF_2	1406	—	—	3070	3140	—

X-*Ray Photography.*—*X*-Ray powder photographs were taken by means of Cu-K_α radiation and a 19-cm. camera; samples were filled into Pyrex capillaries, a " dry-box " being used when necessary, and were sealed with warm picein wax. Lattice constants were evaluated by the methods of Henry, Lipson, and Wooster (" The Interpretation of *X*-ray Diffraction Photographs," Macmillan, 1951). The lines of the sodium fluoroferrate photograph were indexed by analogy with those found by Naray-Szabo and Sasvari (*loc. cit.*) for sodium fluoroaluminate. The corresponding " calculated " and " found " values for $\sin^2\theta$ are :

Sodium fluoroaluminate				Sodiumfluoroferrate		
$\sin^2\theta$ (Mo-K_α)	Int.	$\sin^2\theta$ (converted into Cu-K_α)	Indices	$\sin^2\theta$, found	Int.	$\sin^2\theta$, calc.
0·0061	s	0·0286	011	0·0271	s	0·0274
0·0064	vs	0·0301	101	0·0291	vs	0·0289
0·00827	s	0·0389	{002 / 110}	0·0375	s	0·0375
0·0161	s	0·0756	020	0·0721	w	0·0720
0·0166	vs	0·0780	112	0·0749	s	0·0750
0·01715	s	0·0806	200	0·0776	w	0·0781
0·02125	s	0·0998	210	0·0961	w	0·0961
0·0225	s	0·1058	121	0·1009	w	0·1010
0·0231	vs	0·1086	103	0·1045	m	0·1040
0·0234	s	0·1097	211	—	—	—
0·0256	vs	0·1203	202	—	—	—
0·0272	s	0·1278	113	0·1223	w	0·1220
0·0288	s	0·1353	122	0·1290	w	0·1291
0·0331	vs	0·1556	004	0·1502	s	0·1502
0·0334	vs	0·1570	220			
0·0383	vw	0·1800	031	0·1759	vw	0·1717
0·0403	m	0·1897	130	0·1820	w	0·1818
0·0415	m	0·1953	{114 / 222}	0·1877	m	0·1877
0·0423	w	0·1990	131	0·1915	w	0·1912
0·0492	s	0·2315	024	0·2207	m	0·2223
0·0506	s	0·2380	204	0·2310	m	0·2283
			224	0·2990	vw	0·3004
			304	0·3257	vw	0·3258
			332	0·3740	vw	0·3754

Grateful acknowledgment is made to Dr. R. N. Haszeldine and Dr. N. Sheppard for helpful discussions on infra-red spectra, and to the Department of Scientific and Industrial Research for a Maintenance Grant (to B. C.).

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Anodic Syntheses. Part XI. Synthesis of Tariric and Petroselinic Acid.*

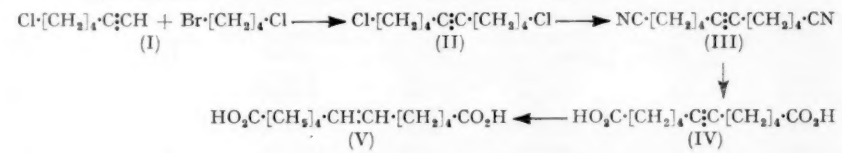
By B. W. Baker, R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon.

[Reprint Order No. 5039.]

Dodec-6-ynedioic acid and the corresponding ethylene, intermediates for the synthesis of unsaturated fatty acids, have been prepared from 6-chlorohex-1-yne.

Tariric acid has been synthesised by anodic "crossed" coupling of methyl hydrogen dodec-6-ynedioate with octanoic acid, and partially reduced to petroselinic acid.

The two preceding papers in this series described the chain extension of unsaturated acids by electrolysis with half esters of dicarboxylic acids. In continuation of this study of anodic routes to long-chain unsaturated fatty acids, the use of components of the type $HO_2C\cdot[CH_2]_n\cdot X\cdot[CH_2]_n\cdot CO_2H$ where X is either an ethylenic or an acetylenic group, is now being examined for the introduction of the unsaturated centre. By "crossed" coupling first at one end of the molecule with a monocarboxylic acid, and then, if desired, at the other with a half ester, a very flexible route to unsaturated acids is available. One minor limitation, which may be inferred from the results of previous workers on the electrolysis of olefinic acids (see a summary by Weedon, *Quart. Reviews*, 1952, **6**, 380), is that n must be >1. In this paper we report the preparation of the previously unknown dodecynedioic (IV) and dodecenedioic † acids (V), and the use of the former for the synthesis of tariric (VII) and petroselinic acid (*cis*-VIII); the last two fatty acids occur in the seed fats of the genus *Picramnia* (Simarubaceae) and of the Umbelliferæ respectively. The synthesis of tariric acid by a different route, and its reduction to petroselinic acid, were recently achieved by Lumb and Smith (*J.*, 1952, 5032).



Condensation in liquid ammonia of the sodio-derivative of 6-chlorohex-1-yne (I) (Newman and Wotiz, *J. Amer. Chem. Soc.*, 1949, **71**, 1294) with tetramethylene bromide chloride gave (45%) the dichlorodecyne (II). This was converted, *via* the corresponding di-iodide, into the dinitrile (III) in 85% overall yield. Hydrolysis then furnished the dodecynedioic acid (IV) in 89% yield. Malonate chain extension of the di-iodide, followed by hydrogenation of the resulting tetra-ester, hydrolysis, and decarboxylation, led to tetradecanedioic acid, which was compared directly with an authentic specimen.

Partial reduction of the dodecynedioic acid over palladium on barium sulphate gave the corresponding ethylenic compound (V) almost quantitatively. From the known stereochemical course of reduction of acetylenes over supported palladium catalysts (cf. Campbell and Campbell, *Chem. Reviews*, 1942, **31**, 148; Crombie, *Quart. Reviews*, 1952, **6**, 128) this product undoubtedly consists very largely, or exclusively, of the *cis*-isomer. Its structure was confirmed by catalytic hydrogenation to dodecanedioic acid, and by oxidative degradation of its dihydroxy-derivative (see below) to adipic acid.

An attempt to prepare *trans*-dodecenedioic acid by reduction of the acetylenic acid with sodium in liquid ammonia (cf. Howton and Davis, *J. Org. Chem.*, 1951, **16**, 1405) was unsuccessful, probably owing to insolubility of the sodium salt of the acid. The inversion of the *cis*-isomer was therefore attempted. Although stereomutation occurred readily on

* Part X, *J.*, 1954, 448.

† The formation of small amounts of dodec-6-enedioic acid, as a by-product in the thermal decomposition of *N*-nitrosohexanolactam, was recently postulated by Heyns and Woyrsch (*Chem. Ber.*, 1953, **86**, 76); it was not isolated, but converted by oxidative degradation into adipic acid.

treatment of *cis*-dodecenedioic acid with nitrous acid, the product melted over a range of 5°, even after repeated crystallisation, and was considered to be contaminated with the *cis*-isomer and/or positional isomers. Inversion of the *cis*-acid by a method very similar to that used by Hunsdiecker (*Ber.*, 1944, **77**, 185) in the eicos-9-enedioic acid series, was somewhat more successful. Oxidation of the *cis*-dodecenedioic acid with performic acid led to 6 : 7-dihydroxydodecanedioic acid, which with a mixture of hydrogen bromide, acetic acid, and sulphuric acid (cf. Ames and Bowman, *J.*, 1951, 1079) gave 6 : 7-dibromododecanedioic acid. By analogy with the products from similar reactions of numerous related compounds, the dihydroxy- and the dibromo-dodecanedioic acid may be assigned the *threo*- and the *erythro*-configuration respectively. Esterification of the dibromo-compound, debromination of the ester with zinc dust, and hydrolysis then furnished the required *trans*-dodecenedioic acid in 23% overall yield from the *cis*-isomer. However this product also melted over a slight range (3°), suggesting some contamination with the *cis*-acid. This is more likely to be due to the presence in the starting material of traces of *trans*-dodecenedioic acid, formed during the partial reduction of the acetylenic acid (cf. Crombie, *loc. cit.*), than by lack of stereospecificity in the various reactions employed in the inversion (cf. Ames and Bowman, *loc. cit.*). The latter possibility cannot, however, be entirely excluded.

$$CH_3\cdot[CH_2]_6\cdot CO_2H + HO_2C\cdot[CH_2]_4\cdot C{:}C\cdot[CH_2]_4\cdot CO_2Me \quad (VI)$$

$$\downarrow$$

$$(VII)\quad CH_3\cdot[CH_2]_{10}\cdot C{:}C\cdot[CH_2]_4\cdot CO_2H \longrightarrow CH_3\cdot[CH_2]_{10}\cdot CH{:}CH\cdot[CH_2]_4\cdot CO_2H \quad (VIII)$$

To illustrate the route to unsaturated fatty acids, dodecynedioic acid (IV) was converted (47%) into the half ester (VI), and the latter was electrolysed with an excess of octanoic acid. By distillation of the mixture of products, formed by both symmetrical and " crossed " coupling of the two components, and subsequent hydrolysis, octadec-6-ynoic acid (VII) was readily isolated in 23% yield. Its m. p. was in excellent agreement with that reported for natural tariric acid (Arnaud, *Compt. rend.*, 1892, **114**, 79; Steger and van Loon, *Rec. Trav. chim.*, 1933, **52**, 593). Partial hydrogenation of the synthetic acid over lead-poisoned palladium * (Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) gave octadec-*cis*-6-enoic acid (VIII), which was identified with natural petroselinic acid by direct comparison. The yield (47%) was very similar to that obtained by Lumb and Smith (*loc. cit.*) who used a Raney nickel catalyst.

Experimental

1 : 10-*Dichlorodec*-5-*yne*.—A solution of sodamide (from 38 g. of sodium) in liquid ammonia (1 l.) (cf. Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120) was added during 2 hr. to a stirred solution of 1-chlorohex-5-yne (200 g.) (Newman and Wotiz, *ibid.*, 1949, **71**, 1294) in liquid ammonia (2 l.). After ½ hr., 1-bromo-4-chlorobutane (300 g.) (Starr and Hixon, *ibid.*, 1934, **56**, 1595) was added during 3½ hr. and the mixture was stirred overnight. Ammonium chloride (100 g.) was added and the ammonia was then evaporated. The residue was extracted thoroughly with ether, and the extract was washed with 2N-hydrochloric acid, then with water, and dried (Na_2SO_4). Distillation yielded: (i) 1 : 10-Dichlorodec-5-yne (153 g.), b. p. 105—113°/1 mm., n_D^{19} 1·4841—1·4858. Analyses of the product from several preparations gave results which were consistently high in carbon and low in chlorine, suggesting that the dichlorodecyne contained small amounts (>10%) of a chlorodecenyne formed by partial dehydrochlorination. (ii) A liquid (35 g.), b. p. 173—176°/0·5 mm., n_D^{19} 1·4970—1·4978.

Dec-5-*yno*-1 : 10-*dinitrile*.—A solution of 1 : 10-dichlorodec-5-yne (110 g.) and sodium iodide (235 g.) in dry acetone (1600 c.c.) was stirred under reflux for 24 hr. After the solid had been filtered off, the solvent was evaporated under reduced pressure. The residue was extracted with ether, and the ethereal solution was washed with aqueous sodium thiosulphate and dried (Na_2SO_4). Evaporation of the ether gave crude 1 : 10-di-iododec-5-yne (192·5 g.). A mixture of the latter, potassium cyanide (98 g.), water (165 c.c.), and acetone (410 c.c.) was vigorously stirred under reflux for 45 hr. About 300 c.c. of the solvent were evaporated, and the residue was extracted with ether. The extract was washed successively with 2N-sodium hydroxide,

* This catalyst was not available when the partial reduction of the dodecynedioic acid was studied. Its use for the reduction of stearolic to oleic acid will be reported in a separate communication.

aqueous sodium thiosulphate, and water, and then dried (Na_2SO_4) and evaporated. Distillation of the residue gave *dec-5-yno*-1 : 10-*dinitrile* (85 g., 85%), b. p. 150—156°/0·6 mm., n_D^{20} 1·4740—1·4755 (Found : C, 76·85; H, 8·4%), which solidified at 0°. Crystallisation from ether–pentane gave a solid, m. p. 19·5—20° (Found : C, 76·6; H, 8·7. $C_{12}H_{16}N_2$ requires C, 76·55; H, 8·55%).

Dodec-6-ynedioic acid.—A mixture of the preceding dinitrile (86 g.), and a solution of potassium hydroxide (110 g.) in water (1 l.) and alcohol (500 c.c.), was stirred vigorously and boiled under reflux until the evolution of ammonia ceased (5 days). The resulting solution was acidified with 6N-hydrochloric acid, and the precipitate thus formed was collected and dried. One crystallisation from benzene gave a micro-crystalline powder (92 g., 89%), m. p. 116—118°. Two further crystallisations from the same solvent gave the *diacid*, m. p. 118·5° (Found : C, 63·95; H, 8·05%; equiv., 114. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%; equiv., 113).

A solution of the preceding diacid (45 g.) and concentrated sulphuric acid (12 g.) in methanol (40 c.c.) and benzene (100 c.c.) was boiled under reflux for 21 hr. Dilution with water and isolation of the product with ether in the usual way gave the *dimethyl ester* (43 g., 86%), b. p. 120°/0·3 mm., n_D^{19} 1·4605 (Found : C, 66·1; H, 8·6. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%).

Methyl Hydrogen Dodec-6-ynedioate.—(a) *Half-esterification method* (cf. Swann, Oehler, and Buswell, *Org. Synth.*, Coll. Vol. II, p. 276). A mixture of dodec-6-ynedioic acid (20 g.), the corresponding methyl ester (13·0 g.), *n*-butyl ether (6 c.c.), concentrated hydrochloric acid (2·5 c.c.), and anhydrous methanol (5·3 c.c.) was heated rapidly to 160°, then boiled gently under reflux at 130° for 2 hr. Methanol (1·7 c.c.) was added, and heating was continued for a further 2 hr. Distillation of the product gave methyl dodec-6-ynedioate (18—20 g.) and the *half-ester* (10·0 g., 47%), b. p. 183—186°/0·6 mm., 157°/0·3 mm., n_D^{20} 1·4689 (Found : C, 65·05; H, 8·55. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·4%). In a smaller-scale experiment, the yield was 54%.

(b) *Half-hydrolysis method* (cf. Signer and Sprecher, *Helv. Chim. Acta*, 1947, **30**, 1001). A solution of methyl dodec-6-ynedioate (35 g.) in methanol (160 c.c) was shaken vigorously for 48 hr. with methanolic N-barium hydroxide (136 c.c., 1 equiv.). The precipitated barium salts were collected, dried, and converted into the sodium salts by shaking them with sodium sulphate (11·5 g.) in water (440 c.c.). The mixture was filtered, and the solution of sodium salts was acidified with dilute hydrochloric acid. The resulting flocculent precipitate (19·7 g.) was collected, and crystallised from benzene, giving dodec-6-ynedioic acid (5·6 g.). Evaporation of the benzene mother-liquors yielded the half-ester (10·5 g., 32%), b. p. 110° (bath-temp.)/10^{-5} mm., m. p. 22·3—22·9° (Found : equiv., 235. Calc. for $C_{13}H_{20}O_4$: equiv., 240). The benzylamine salt melted below 20°, and neither the piperazine nor the morpholine salt could be purified.

Dodec-cis-6-*enedioic Acid.*—A solution of dodec-6-ynedioic acid (21·9 g.) in dioxan (250 c.c.) was shaken in hydrogen in the presence of palladium on barium sulphate (2·5 g.; 0·3% of Pd). When 1 mol. of hydrogen had been taken up, the rate of absorption dropped markedly, and the reaction was interrupted. Removal of catalyst and solvent, and crystallisation of the residue from 50% aqueous methanol, gave the *diacid* (20 g.), m. p. 60·5—61·5° (Found : C, 63·1; H, 8·85. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·85%). The *benzylamine* salt crystallised from dioxan and from ethyl acetate and had m. p. 124·5—125·5° (Found : C, 70·3; H, 8·75. $C_{26}H_{38}O_4N_2$ requires C, 70·55; H, 8·65%). After generation from this salt, and one crystallisation from aqueous methanol, the diacid had m. p. 62—63·5°.

Reduction of methyl dodec-6-ynedioate in ethyl acetate over palladium on calcium carbonate (0·3% of Pd), and interruption of the reaction after 1 mol. of hydrogen had been absorbed, gave a mixture.

Dodecanedioic Acid.—A solution of the preceding diacid (0·15 g.) in dioxan (15 c.c.) was shaken in hydrogen in the presence of Adams catalyst until absorption was complete. Removal of catalyst and solvent, and crystallisation of the residue first from ethyl acetate and then from water, gave dodecanedioic acid (0·07 g.) as plates, m. p. 127·5—128·5° (Walker and Lumsden, *J.*, 1901, **79**, 1200, give m. p. 126·5—127°).

threo-6 : 7-*Dihydroxydodecanedioic Acid* (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786).—Hydrogen peroxide (5·85 g.; 90—100-vol.) was added in one portion to a stirred solution of dodec-*cis*-6-enedioic acid (10·0 g.) in formic acid (36 c.c.; 98—100%) at 40°. The mixture was stirred at 40° for 4½ hr. and the formic acid was then removed by steam-distillation (1½ hr.). Evaporation of the residue under reduced pressure, and crystallisation from ethyl acetate, gave threo-6 : 7-*dihydroxydodecanedioic acid* (5·3 g., 46%), m. p. 125·5—127·5° (Found : C, 55·35; H, 8·65. $C_{12}H_{22}O_6$ requires C, 54·95; H, 8·45%).

Oxidation of threo-6 : 7-*Dihydroxydodecanedioic Acid.*—A solution of periodic acid (1·2 g.) in water (60 c.c.) was added to one of *threo*-6 : 7-dihydroxydodecanedioic acid (1·0 g.) in water (70 c.c.) at 40°. The mixture was kept at 20° for 3 hr., then diluted with water (to 250 c.c.) and thoroughly extracted with ether. The extract was evaporated and the liquid residue was treated, in 2N-sulphuric acid at 50°, with excess of solid potassium permanganate. The suspension was kept at 50° for 2 hr. and then treated with excess of sulphur dioxide. Concentration of the resulting solution yielded a solid (0·7 g., 64%), which was crystallised from ethyl acetate, giving adipic acid, m. p. and mixed m. p. 149—151°.

Dodec-trans-6-*enedioic Acid.*—(*a*) Concentrated sulphuric acid (6 c.c.) was added in small portions to a cooled solution of *threo*-6 : 7-dihydroxydodecanedioic acid (5·0 g.) in hydrogen bromide–acetic acid (61 c.c.; 20% w/v). The mixture was kept at 20° for 42 hr., and then heated at 100° for 7½ hr. (after 4 hr. a further 6·5 c.c. of hydrogen bromide–acetic acid was added) and again cooled. Water was added, and the resulting precipitate was collected. Crystallisation from benzene gave erythro-6 : 7-*dibromododecanedioic acid* (6·0 g., 81%), m. p. 133—136° (Found: C, 37·15; H, 5·35; Br, 41·25. $C_{12}H_{20}O_4Br_2$ requires C, 37·15; H, 5·2; Br, 41·2%).

Azeotropic esterification of the dibromo-diacid (4·7 g.) gave the corresponding diethyl ester (4·95 g., 93%). A solution of this ester in alcohol (60·5 c.c.) was boiled under reflux and stirred vigorously for 1 hr. with activated zinc dust (12·1 g.) in an atmosphere of nitrogen. Filtration and isolation of the product with light petroleum (b. p. 60—80°) in the usual way gave *ethyl dodec*-trans-6-*enedioate* (2·5 g., 79%), b. p. 95—110°/0·1 mm., $n_D^{21\cdot5}$ 1·4491 (Found: C, 67·45; H, 9·95. $C_{16}H_{28}O_4$ requires C, 67·55; H, 9·9%). Hydrolysis of the diester (2·4 g.) with aqueous-methanolic potassium hydroxide (*ca.* 10% w/v) in an atmosphere of nitrogen gave *dodec*-trans-6-*enedioic acid* (1·6 g., 83%), which crystallised from aqueous methanol as plates, m. p. 134—137° (Found: C, 63·05; H, 8·9. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·85%).

(*b*) By elaidinisation. Dodec-*cis*-6-enedioic acid (1·0 g.) was mixed with a solution of sodium nitrite (65 mg.) in water (0·25 c.c.), and the mixture was heated to 80°, whereupon it became homogeneous. Nitric acid (0·6 c.c.; 35% w/w) was added and the solution was stirred rapidly. After 1 min. the solution solidified and heating was discontinued. Crystallisation of the solid from benzene gave plates (318 mg.), m. p. 122—135°. Subsequent crystallisation from benzene, then from aqueous methanol, and finally from ethyl acetate, gave the diacid, m. p. 130—135°, not raised by further crystallisation (Found: C, 63·0; H, 9·0%).

Ethyl Dodec-6-*ynetetracarboxylate.*—1 : 10-Di-iododec-5-yne, prepared as described above from the dichloro-compound (25 g.), in absolute alcohol (80 c.c.) was added to a boiling and vigorously stirred solution of ethyl sodiomalonate (from 5·0 g. of sodium and 34·5 g. of ethyl malonate) in alcohol (85 c.c.). The mixture was stirred and heated under reflux for 15 hr. and then cooled and filtered. The filtrate was concentrated under reduced pressure and then poured into water. Isolation of the product with ether and distillation gave a liquid (5·0 g.), b. p. 170—205°/0·2 mm., n_D^{21} 1·4640, which contained iodine, and the *tetra-ester* (25 g., 50%), b. p. 155—165° (bath-temp.)/10^{-5} mm., n_D^{22} 1·4590 (Found: C, 63·05; H, 8·4. $C_{24}H_{38}O_8$ requires C, 63·4; H, 8·45%).

Tetradecanedioic Acid.—A solution of the tetra-ester (295 mg.) in ethyl acetate (16 c.c.) was shaken with Adams catalyst (26 mg.) in an atmosphere of hydrogen until absorption ceased (34·2 c.c. at 23°/772 mm., equiv. to 2·2 double bonds). After removal of the catalyst and solvent, the residue was hydrolysed with aqueous-methanolic potassium hydroxide, giving the tetra-acid. This was heated to 165° until the evolution of carbon dioxide was complete. Crystallisation of the residue (120 mg., 71%) from aqueous ethanol gave tetradecanedioic acid, m. p. and mixed m. p. 124—125·5° (Chuit, Boelsing, Hausser, and Malet, *Helv. Chim. Acta*, 1927, **10**, 113, give m. p. 124·8—125·4°).

Octadec-6-*ynoic Acid* (*Tariric Acid*).—Octanoic acid (7·2 g., 3 mols.; equiv., 144) and methyl hydrogen dodec-6-ynedioate (4·0 g., 1 mol.) were added to a solution of sodium methoxide (from *ca.* 30 mg. sodium) in methanol (25 c.c.). The solution was electrolysed in cell "A" (cf. Part X) (current 1·3—1·5 amp.; faradays passed *ca.* 1·25 times theoretical), the temperature of the electrolyte being kept below 50°. Towards the end of the reaction, when the current began to drop, a further quantity of octanoic acid (2·4 g., 1 mol.) was added and the electrolysis was continued until the electrolyte became slightly alkaline. The cell contents were then acidified with 2N-hydrochloric acid, and the solvent was removed under reduced pressure. The residue, in ether, was washed with 0·5N-sodium hydroxide, and water, and then dried ($MgSO_4$). Distillation gave tetradecane (3·4 g., 51%), b. p. 60—64°/3 × 10^{-3} mm., n_D^{24} 1·4310, and a mixture of esters (2·4 g.), b. p. 132—156°/3 × 10^{-3} mm., n_D^{25} 1·4462—1·4558. Hydrolysis of

the latter with aqueous-alcoholic potassium hydroxide (10%) gave the crude acid, which after crystallisation from light petroleum (b. p. 40—60°) and from aqueous alcohol yielded octadec-6-ynoic acid as needles (1·1 g.), m. p. 50·0—50·5° (corr.) (for tariric acid, Arnaud, *Compt. rend.*, 1892, **114**, 79, and Steger and van Loon, *Rec. Trav. chim.*, 1933, **52**, 593, give m. p. 50·5°) (Found: C, 76·8; H, 11·55%; equiv., 279. Calc. for $C_{18}H_{32}O_2$: C, 77·1; H, 11·5%; equiv., 280). The hydrogen no. was 143, equiv. to 1·95 double bonds. The di-iodide, prepared by the method of Arnaud and Posternak (*Compt. rend.*, 1909, **149**, 220), crystallised from glacial acetic acid in clusters of needles (37%), m. p. 37—38°, containing solvent of crystallisation (Lumb and Smith, *J.*, 1952, 5032, give m. p. 37—38°). By keeping the product under reduced pressure over potassium hydroxide the solvent-free di-iodide was obtained and had m. p. 47—48° (Arnaud and Posternak, *loc. cit.*, give m. p. 48·5°).

Electrolysis of the half-ester (8·5 g.) in methanol (30 c.c.) was accompanied by the deposition on the electrodes of large amounts of polymeric material. Isolation of the product in the usual way gave *docosa*-6 : 16-*diynedioic acid* which crystallised from aqueous methanol in plates (54 mg.), m. p. 102—104° (Found: C, 73·2; H, 9·6. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·45%). The diacid (8·821 mg.) in acetic acid was shaken in hydrogen with Adams catalyst until absorption was complete (2·038 c.c. at N.T.P., equiv. to 3·75 double bonds). Removal of catalyst and solvent, and crystallisation of the residue from alcohol, gave docosanedioic acid, m. p. 124·5—125·5°, undepressed on admixture with an authentic specimen.

Octadec-cis-6-*enoic Acid* (*Petroselinic Acid*).—A solution of octadec-6-ynoic acid (253 mg.) in ethyl acetate (25 c.c.) and quinoline (103 mg.) was shaken in hydrogen in the presence of a lead-poisoned palladium-on-calcium carbonate catalyst (255 mg.; Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446) until absorption ceased (20 c.c. at 18°/758 mm.; 0·93 mol.). The catalyst was removed by filtration through kieselguhr, and the filtrate was washed with 2N-hydrochloric acid (to remove quinoline), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure and crystallisation of the residue from light petroleum (b. p. 60—80°) and from aqueous alcohol, gave octadec-*cis*-6-enoic (121 mg.), m. p. 28·7—29·4° (corr.), raised by further crystallisation to 29·0—29·5°. A mixture with a specimen of natural petroselinic acid, m. p. 28·4—28·8° (kindly supplied by Dr. J. H. Skellon), from parsley oil had m. p. 28·6—29·0° (van Loon, *Rec. Trav. chim.*, 1927, **46**, 492, gives m. p. 29·4°).

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Reactions of cyclo*Octatetraene. Part V.* Selective Reduction by Metals and Alkalis or Acids.*

By William O. Jones.

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*cyclo*Octatetraene has been reduced to *cyclo*octene by treatment with Raney nickel alloy in dilute sodium hydroxide. Reduction by zinc dust in sodium hydroxide or in aqueous-alcoholic sulphuric acid gave good yields of *cyclo*octatrienes, principally the 1 : 3 : 6-triene. With alcoholic potassium hydroxide and zinc dust, however, the main constituent was *cyclo*octa-1 : 3 : 5-triene. Addition of halogens to the *cyclo*octatrienes has been examined, and the silver nitrate adducts of *cis-cyclo*octene and of *cyclo*octa-1 : 3 : 6-triene have been prepared.

After our studies * on the reduction of *cyclo*octatetraene with sodium and alcohol, we examined its behaviour on treatment with Raney nickel alloy in hot aqueous alkali without the addition of external hydrogen (cf. Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366). This might be expected to be equivalent to hydrogenation with a Raney nickel catalyst, since the latter, together with hydrogen, is produced *in situ*. Reppe (FIAT Final

* Part IV, *J.*, 1954, 312.

Report No. 967, p. 85) found catalytic reduction of *cyclo*octatetraene with Raney nickel to give *cyclo*octane even more rapidly than with platinum catalysts, there being presumably no sign of selective reduction to *cyclo*octene as is the case with palladium catalysts. However, with Raney alloy and alkali, without added hydrogen, reduction does not proceed beyond *cyclo*octene. The product (n_D^{20} 1·4730, f. p. −25°), after one treatment, contained 90—95% of *cyclo*octene, 4—9% of *cyclo*octadienes, and (probably) about 1% of *bicyclo*[4 : 2 : 0]octane. By extraction with 50% aqueous silver nitrate, most of the dienes were removed at 70° and the bulk of the *cis-cyclo*octene at 40—45°, the bicyclic hydrocarbon remaining in the residue. A crystalline adduct, $2C_8H_{14},AgNO_3$ (m. p. 51°), of *cis-cyclo*octene was isolated. Cope, Pike, and Spencer (*J. Amer. Chem. Soc.*, 1953, **75**, 3212) reported that *trans-cyclo*octene can be extracted from pentane solution by 20% aqueous silver nitrate, but the *cis*-isomer did not react under these conditions.

The *cyclo*octadienes produced in the Raney alloy reduction were only slowly reduced to *cyclo*octene by further reaction with Raney alloy and sodium hydroxide (3 or 4 more treatments required). This is in marked contrast to the behaviour of the *cyclo*octadienes which are formed *en route* to *cyclo*octene by the normal catalytic process, *e.g.*, with palladium on barium sulphate in methanol; these dienes are readily reduced to *cyclo*octene by one treatment with Raney alloy and sodium hydroxide. This suggests that different stereoisomeric dienes are present in the two cases. In this connection, Ziegler and Wilms (*Annalen*, 1950, **567**, 14) have reported that the labile isomer of *cyclo*octa-1 : 5-diene is hydrogenated to *cyclo*octene twice as fast as the stable isomer.

In aqueous sodium hydroxide *cyclo*octatetraene was not reduced when aluminium powder was employed instead of Raney alloy, although reduction to *cyclo*octatrienes occurred in alcoholic alkali. It is evident therefore that the presence of the nickel in the Raney alloy is necessary for reduction beyond the *cyclo*octatriene stage.

Reduction of *cyclo*octatetraene to *cyclo*octatrienes was first effected by Reppe, Schlichting, Klager, and Toepel (*Annalen*, 1948, **560**, 1) by treating its dilithium adduct with methanol. The complex nature of the products of this reaction was demonstrated by Cope *et al.* (*J. Amer. Chem. Soc.*, 1950, **72**, 2515; 1952, **74**, 4867) who also described improved methods of reduction in which *cyclo*octatetraene was treated in liquid ammonia with sodium and then with ammonium chloride. Cope and his co-workers also showed that the partly unconjugated 1 : 3 : 6-isomer (I) rearranges to the fully conjugated 1 : 3 : 5-isomer (II) when heated with potassium *tert.*-butoxide, and that *cyclo*octa-1 : 3 : 5-triene is normally in mobile equilibrium with the bridged isomer, *bicyclo*[4 : 2 : 0]octa-2 : 4-diene (III) [85% of (II) and 15% of (III) at equilibrium].

We now find that reduction of *cyclo*octatetraene with zinc dust in aqueous-alcoholic caustic alkali does not proceed beyond the *cyclo*octatriene stage, the main constituent being (I) when sodium hydroxide was used and (II) [in equilibrium with (III)] when potassium hydroxide was used. Since (I) is readily isomerised to (II) by alcoholic potassium hydroxide it is probable that the former is the primary product with either alkali. The silver nitrate adduct of (I), $C_8H_{10},3AgNO_3$, m. p. 139°, was formed from the trienes obtained by use of sodium hydroxide. Pure (I) was obtained by treating the adduct with aqueous ammonia. Cope and Hochstein (*J. Amer. Chem. Soc.*, 1950, **72**, 2515) have described material which was contaminated with 4—6% of (II).

The product (n_D^{25} 1·5110) initially isolated on use of sodium hydroxide was easily converted into the equilibrium mixture of (II) and (III) (n_D^{25} 1·5223) by hot alcoholic potassium hydroxide. Alternatively, *cyclo*octatetraene was converted in one step into the same equilibrium mixture, simply by heating it for a short time on the steam-bath with zinc dust and alcoholic potassium hydroxide.

In view of the above results we examined the reduction with zinc in an acid medium. Craig, Elofson, and Ressa (*ibid.*, 1953, **75**, 481) reported that reduction proceeds to a limited

extent with zinc and acetic acid, but the products were not isolated, ultra-violet absorption curves suggesting that *cyclo*octatrienes were present. It has now been found that with zinc and sulphuric acid in 75% ethanol reduction proceeds only as far as *cyclo*octatriene, the principal constituent of the product (n_D^{25} 1·5088) being (I).

An adduct, m. p. 140—142°, was formed when *cyclo*octa-1 : 3 : 6-triene was heated with maleic anhydride at 140—150° and was shown (by mixed m. p. determinations) to be identical with the known adduct from (II) or from (III) (Reppe *et al.*, *loc. cit.*; Cope *et al.*, *loc. cit.*, 1952). It follows that isomerisation of (I) to (II) and/or (III) must have taken place. This was confirmed by heating (I) (n_D^{25} 1·5050) at 140—150° for one hour, which caused a change in refractive index to n_D^{25} 1·5240, and from which the silver nitrate adduct of (II) was readily obtained. There was no detectable isomerisation of (I) at 100° (1 hr.).

Unlike *cyclo*octatetraene, which rearranges to a bicyclic system on halogenation (Reppe *et al.*, *loc. cit.*) the *cyclo*octatrienes maintained their eight-membered ring, at least to a very large extent. Both trienes yielded a mixture of tetra- and hexa-chlorides (in a molar ratio of 1 : 3) on treatment with an excess of chlorine at −20°. At higher temperatures (20°) and with a larger excess of chlorine, substitution also occurred, to give heptachlorides. On bromination at 0°, a mixture of tetra- and hexa-bromides could be obtained from (II), whereas (I) gave only tetrabromides. The latter, however, added chlorine slowly, which indicates that the tetrabromides are tetrabromo*cyclo*octenes rather than *bicyclo*[4 : 2 : 0]-octane derivatives. The halogenation products are believed to consist of mixtures of stereoisomers, and from the various halogenations a number of individual isomers have been isolated in crystalline form.

Experimental

Reduction of cyclo*Octatetraene with Raney Nickel Alloy and Sodium Hydroxide.*—(*a*) *cyclo*Octatetraene (15 g.) and 10% aqueous sodium hydroxide (500 ml.) were stirred rapidly in a 2-l. flask at 80—90°, and Raney alloy (50 g.) was added during 2 hr. The crude *cyclo*octene (15 g.; n_D^{20} 1·4751, f. p. −23°) was recovered by steam-distillation.

(*b*) *cyclo*Octatetraene (104 g.), ethanol (1 l.), and Raney alloy (162 g.) were stirred at the b. p., and 20% sodium hydroxide solution (900 ml.) was added at such a rate that the heat of reaction maintained the mixture at the boil. The product (b. p. 54—55°/50 mm., f. p. −30°, n_D^{20} 1·4740) was isolated by addition of water (2 l.), washed until alkali-free, dried ($CaCl_2$), and distilled.

(*c*) A 1-l. stainless-steel rotating autoclave was charged with Raney alloy (37 g.), *cyclo*octatetraene (33 g.), and 10% aqueous sodium hydroxide (350 ml.), the latter being contained in a glass liner to avoid mixing until after closure. The autoclave was rolled for 3 hr., no external heat being applied. The temperature reached 46° and the pressure 220 lb./sq. in. in 10 min. and then decreased slowly (33°/15 lb. after 1·5 hr.). The product (n_D^{20} 1·4730, f. p. −24°) was isolated as in (*a*). Catalytic hydrogenation (Adams catalyst in acetic acid) showed the presence of 5% of *cyclo*octadienes and yielded *cyclo*octane, m. p. 11·5°, n_D^{20} 1·4568, of approx. 98% purity (cf. Cope and Hochstein, *loc. cit.*).

The f. p.s of crude *cis-cyclo*octene (−23° to −30°) prepared by the above methods compare with −12° for the pure compound (Ziegler and Wilms, *loc. cit.*). By subjecting a material of f. p. −30°, n_D^{20} 1·4750, to four further treatments with Raney alloy and sodium hydroxide its f. p. was raised only to −22° (n_D^{20} 1·4705; 0·97 mol. of hydrogen absorbed on catalytic hydrogenation). On the contrary, crude *cis-cyclo*octene (20 g.; f. p. −22°; containing 10% of *cyclo*octadienes) which had been prepared by catalytic hydrogenation of *cyclo*octatetraene (Pd–$BaSO_4$ catalyst; no diluent) had f. p. −14° after one treatment with Raney alloy (50 g.) and 10% aqueous sodium hydroxide (500 ml.).

Preparation of the Silver Nitrate Adduct of cis-cyclo*Octene.*—Crude *cyclo*octene [40 ml.; obtained by catalytic hydrogenation (Pd–$BaSO_4$) of *cyclo*octatetraene in the absence of a diluent] was shaken at 70—80° with 50% (w/w) silver nitrate solution (2 × 15 ml.) to remove *cyclo*octadienes (aqueous layer). Extraction was continued at 40° (4 × 20 ml.), three layers now being formed each time, the middle layer being the silver nitrate adduct of *cis-cyclo*octene, which crystallised (m. p. 38°) on separation and cooling to room temperature. The *adduct* was highly soluble in methanol (at least 1 g. in 1 ml.), from which it crystallised (at 0°) in large flat needles which were dried during one week under a slight vacuum over calcium chloride and *cyclo*octene saturated with paraffin wax. The product (m. p. 51°) lost hydrocarbon rapidly on exposure to air (Found: C, 48·8; H, 7·2; Ag, 27·4. $2C_8H_{14},AgNO_3$ requires C, 49·2; H, 7·2; Ag, 27·7%).

Approximate Separation of Components of Crude cyclo*Octene by Means of Silver Nitrate.*—When crude *cyclo*octene (35 ml.) from a Raney alloy reduction [sample from (*b*) above] was subjected to a similar treatment with silver nitrate, an oil (1·7 ml.; n_D^{20} 1·4675) remained after the *cyclo*octadienes (2·5 ml.) and most of the *cyclo*octene had been removed. It absorbed 0·72 mol. of hydrogen to give an impure *cyclo*octane (n_D^{20} 1·4582, f. p. −15°). These results suggest that the oil was a mixture of *cyclo*octene (72%) and *bicyclo*octane (28%), the estimated refractive indices (20°) of such a mixture before and after hydrogenation being 1·4671 and 1·4589 respectively.

Reduction of cyclo*Octatetraene to* cyclo*Octatrienes by Means of Sodium Hydroxide and Zinc Dust.*—(*a*) The following materials were charged into a 1-l. stainless steel rocking autoclave: *cyclo*octatetraene (104 g.), zinc dust (130 g.), sodium hydroxide (160 g. in 320 g. of water), ethanol (200 ml.), and platinum chloride (4 drops of a 2% aqueous solution, for activating the zinc). The contents were heated at 90—100° for 3 hr. The product consisted of a grey mass of needles and an orange liquid and was steam-distilled, yielding a very pale yellow oil (principally *cyclo*octa-1 : 3 : 6-triene; 92 g.; n_D^{25} 1·5150; 0·12% of *cyclo*octatetraene by polarography).

(*b*) *cyclo*Octatetraene (50 g.), zinc dust (130 g.), ethanol (600 ml.), and water (60 ml.) were stirred rapidly on the steam-bath, and sodium hydroxide solution (160 g. in 640 ml. of water) was added dropwise during 1 hr. After a further 2½ hr. the product was isolated by steam-distillation. The bulk of the product was colourless (39 g.; n_D^{25} 1·5107), but towards the end of the distillation the product was very pale yellow and this portion was discarded. On hydrogenation (Pd–$CaCO_3$ in methanol) 2·85 mols. of hydrogen were absorbed (a sharp break occurring at 1·96 mols.), and *cyclo*octane, m. p. 8—9°, n_D^{25} 1·4568 (97·5% purity), was produced.

Isomerisation of the cyclo*Octa*-1 : 3 : 6-*triene Component of the Mixed Trienes.*—(*a*) A mixture of trienes (5 g.; n_D^{25} 1·5120) was treated with potassium (0·1 g.) and *tert.*-butanol (20 ml.) on the steam-bath for 2 hr. A dark brown colour was produced immediately on mixing and a small quantity of resin separated. The oil obtained on steam-distillation had n_D^{25} 1·5175. (*b*) By heating the mixed trienes (50 g.; n_D^{25} 1·5150) with alcoholic potassium hydroxide (66 g. of alkali in 300 ml. of ethanol) in an autoclave at 90—100° for 4 hr. a product with n_D^{25} 1·5223 was obtained (2·76 mols. of hydrogen absorbed over Pd–$CaCO_3$ in methanol), which yielded the adduct (m. p. 123—125°) of (II) with 50% silver nitrate solution.

Reduction of cyclo*Octatetraene to* cyclo*Octa*-1 : 3 : 5-*triene* (II).—A mixture of *cyclo*octatetraene (5 g.), ethanol (40 ml.), zinc dust (10 g.), and potassium hydroxide (10 g.) was heated on the steam-bath in nitrogen. There was no appreciable reaction until 2—3 drops of aqueous platinum chloride (4% solution) were introduced. Heating was continued for 3 hr. with occasional shaking, and the mixture was then steam-distilled. The product (5 g.) consisted of a colourless oil, n_D^{25} 1·5220, which gave an 85% yield of the silver nitrate adduct (m. p. 123—125°) of (II) and absorbed 2·8 mols. of hydrogen on catalytic hydrogenation (Pd–$CaCO_3$ in acetic acid), the resulting *cyclo*octane having m. p. 7—8°, n_D^{25} 1·4568, purity 97%.

The product was yellow when nitrogen had been omitted, and towards the end of the steam-distillation a viscous yellow oil and a pale yellow solid appeared, the latter probably the oxygen addition compound of (II) (Cope and Hochstein, *loc. cit.*, 1950). This solid decomposed vigorously on being heated, and was insoluble in ether and in benzene, and soluble in hot aqueous sodium hydroxide [Found: C, 67·9; H, 6·7. Calc. for $(C_8H_{10}O_2)_x$: C, 69·5; H, 7·3%].

When the experiment was carried out with aqueous potassium hydroxide, *cyclo*octatetraene was converted in 3 hr. into a product with n_D^{25} 1·5187. After a further 8 hr. the pale yellow product had n_D^{25} 1·5215, which suggested that its composition was close to that of the equilibrium mixture of (II) and (III). Treatment with 50% aqueous silver nitrate, however, gave only a small yield of the adduct of (II), whereas a high yield was obtained from an authentic equilibrium mixture.

Presence of Raney nickel (1 g.) during the reaction in alcoholic potassium hydroxide enabled the reduction to proceed beyond the *cyclo*octatriene stage, the product having n_D^{25} 1·5025 and 1·4705 after 3 and 9 hr., respectively.

Aluminium powder was not as effective in the formation of trienes as zinc dust, no reduction being observed in aqueous-alcoholic sodium hydroxide, whilst the product (n_D^{25} 1·5208) formed (in 2 hr.) in alcoholic potassium hydroxide remained pale yellow and gave only a small yield of the adduct of (II) with 50% silver nitrate solution. *cyclo*Octatetraene was not affected by pin dust and hydrochloric acid in boiling ethanol.

Reduction of cyclo*Octatetraene by Means of Zinc Dust and Aqueous-alcoholic Sulphuric Acid.*—A mixture of zinc dust (30 g.), *cyclo*octatetraene (20 ml.), and ethanol (250 ml.) was boiled on the steam-bath, and 50% (w/w) sulphuric acid (100 ml.) containing 3 drops of 4% platinum chloride

was added dropwise during 0·5 hr. A sample isolated after 4 hours' heating had a pale yellow colour and n_D^{25} 1·5150. After the addition of more zinc dust (30 g.), ethanol (250 ml.), and sulphuric acid (100 ml.; 50% w/w) the main portion was heated again for 6 hr. The supernatant liquid was poured into water (2 l.), and the pale yellow oil was separated, washed, and dried ($CaCl_2$). Distillation yielded a colourless product (n_D^{25} 1·5088; f. p. $< -70°$), which gave the adduct (m. p. 139°) of *cyclo*octa-1 : 3 : 6-triene with silver nitrate in ethanol. On catalytic hydrogenation, 2·7 mols. of hydrogen were absorbed by the crude triene, to yield *cyclo*octane of f. p. 1—2° (95% purity).

Purification of cyclo*Octa*-1 : 3 : 6-*triene* (I) *through its Silver Nitrate Adduct.*—The mixed hydrocarbons (12 g.; n_D^{25} 1·5150) obtained by the action of zinc dust and aqueous-alcoholic sodium hydroxide on *cyclo*octatetraene were boiled with ethanol (150 ml.) and powdered silver nitrate (58 g.) and filtered hot. The *adduct* (25 g.) obtained on cooling formed flat needles, m. p. 138—139°, from methanol (Found: C, 15·8; H, 1·6. $C_8H_{10},3AgNO_3$ requires C, 15·6; H, 1·6%). The original mother-liquor very slowly deposited a second crop of crystals, the majority of which were small needles but which also contained a few large rectangular crystals shown (after hand-separation and recrystallisation, mixed m. p.) to be the adduct of (II).

The complex from (I) was decomposed by adding it to an excess of dilute aqueous ammonia at room temperature. The liberated oil was washed, and dried ($CaCl_2$). Pure *cyclo*octa-1 : 3 : 6-triene obtained in this way had n_D^{25} 1·5050, f. p. −52° (Found: C, 90·8; H, 9·4. Calc. for C_8H_{10}: C, 90·5; H, 9·5%). Cope and Hochstein (*loc. cit.*) gave n_D^{25} 1·5046, f. p. −56° to −62° for slightly impure material. On hydrogenation in methanol (Pd–$CaCO_3$), 1·96 mols. were absorbed very rapidly, and hydrogen uptake ceased at 2·94 mols. The refractive index of (I) was unchanged after 1 hr. on the steam-bath, but heating for 1 hr. at 150° caused its value to rise to 1·5240 (25°). The resulting product gave a high yield of the adduct of (II) on treatment with aqueous silver nitrate (m. p. and mixed m. p. 123—125°). (I) did not form an adduct with maleic anhydride in benzene at room temperature (in presence of a trace of trichloroacetic acid), but at 140—150° in the absence of a solvent an adduct, m. p. 145—146°, was obtained, identical with the maleic anhydride adduct of (II) (mixed m. p.).

The isomeric trienes (I) and (II) differ appreciably in their behaviour with silver nitrate. With an aqueous solution of the reagent (50% w/w), the complex with *cyclo*octa-1 : 3 : 5-triene was precipitated immediately in excellent yield, whilst that from (II) did not separate even after several hours at 0° (an exothermic reaction on mixing, and the formation of a homogeneous solution showed that adduct formation had occurred). When the aqueous silver nitrate mixtures were warmed the adduct from (III) appeared to be stable up to 70—75° at which point the solid disappeared and a hydrocarbon layer was formed on the surface; the solution containing (II) became milky at 40°. Both trienes form beautifully crystalline adducts with powdered silver nitrate in ethanol. The complex from (III) lost hydrocarbon on exposure to air much more quickly than did that from (II). Pure *cyclo*octa-1 : 3 : 5-triene regenerated from its adduct by means of cold aqueous ammonia had n_D^{25} 1·5245 (f. p. $< -70°$). in good agreement with the value recorded by Cope *et al.*, *loc. cit.*, 1952).

Addition of Bromine to cyclo*Octa*-1 : 3 : 5-*triene.*—(*a*) The triene (2·84 g.) in carbon tetrachloride (100 ml.) was treated at 0° with bromine (2·5 mols.) in the same solvent (110 ml.). The first mol. of bromine was absorbed instantly, but after one week the total uptake was only 1·9 mols. The excess of bromine was removed with aqueous sodium hydrogen sulphite, and the solution was washed and dried (Na_2SO_4). A colourless oil (10·7 g., 94% yield as tetrabromides) was left after removal of the solvent. A portion (1·0 g.) of the product was obtained in a solid form by keeping a solution in light petroleum (b. p. 60—80°) at 0—10° for 2—3 hr. The *tetrabromide* (possibly 3 : 4 : 7 : 8-tetrabromo*cyclo*octene), recrystallised from methanol, had m. p. 169—170° (Found: C, 22·6; H, 2·3; Br, 75·2. $C_8H_{10}Br_4$ requires C, 22·6; H, 2·4; Br, 75·1%).

(*b*) By employing twice as much bromine, a semisolid mixture of tetra- and hexa-bromides (21 g. from 5 g. of triene) was obtained, which yielded 1 : 2 : 3 : 4 : 5 : 6-*hexabromo*cyclo*octane* (9·9 g.) on trituration with methanol; this formed colourless prisms, m. p. 149°, from *iso*propanol or from benzene–light petroleum (Found: C, 16·0; H, 1·8; Br, 82·5. $C_8H_{10}Br_6$ requires C, 16·4; H, 1·7; Br, 81·9%).

Addition of Bromine to cyclo*Octa*-1 : 3 : 6-*triene.*—This hydrocarbon (1·59 g.) was treated with bromine as in (*a*), 1 mol. of bromine being absorbed immediately and a second in 3 days. The viscous oily product (6·5 g.) consisted of tetrabromides (Found: C, 22·6; H, 2·4%) from which one *isomer* (0·9 g.) was obtained in a crystalline form from ethyl acetate. It formed colourless prisms (m. p. 121°) from benzene (Found: C, 22·6; H, 2·4; Br, 75·1%). The remainder of the

material was chromatographed (light petroleum–alumina), but no other solid isomer could be isolated.

On use of a large excess of bromine [as in (*b*) above], the product was again essentially tetrabromide (Found : C, 21·8; H, 2·3%). Treatment with a large excess of chlorine in carbon tetrachloride for one week at 20° resulted in addition and some substitution (Found : C, 17·7; H, 1·9. Calc. for $C_8H_9Cl_3Br_4$: C, 18·1; H, 1·7%).

Addition of Chlorine to cyclo*Octa*-1 : 3 : 5-*triene*.—(*a*) The pure triene (6 g.) was treated in chloroform (75 ml.) at −20° with chlorine until the increase in weight was 14 g. The excess of chlorine and the solvent were removed after 16 hr. at 0° (14·5 g.) (Found : C, 31·9; H, 3·2; Cl, 64·6%). The oily mixture of hexa- and tetra-chlorides on chromatography [alumina; light petroleum (b. p. 60—80°) containing 1% of benzene] yielded very small quantities of two isomeric *tetrachlorides*, (i) colourless needles (from methanol), m. p. 92—93° (Found : C, 37·7; H, 4·2; Cl, 57·9. $C_8H_{10}Cl_4$ requires C, 38·7; H, 4·1; Cl, 57·2%), and (ii) colourless needles (from methanol), m. p. 168° (Found : C, 38·7; H, 4·2%).

Some substitution occurred on chlorination at 20° (4 days), the colourless oil, n_D^{17} 1·5600, approximating to a heptachloride (Found : C, 27·6; H, 2·6. Calc. for $C_8H_9Cl_7$: C, 27·2; H, 2·6%).

(*b*) Addition of 2 mols. of chlorine to (II) yielded a colourless oil, b. p. 119—120°/1 mm., n_D^{17} 1·5596 (Found : C, 38·5; H, 4·0%), but the only solid obtained on chromatography was the tetrachloride, m. p. 168° (approx. 1% of the original product).

Addition of Chlorine to cyclo*Octa*-1 : 3 : 6-*triene*.—*cyclo*Octa-1 : 3 : 6-triene (3·9 g.) gave a mixture (9 g.) of hexa- and tetra-chlorides (Found : C, 32·0; H, 3·3%) on chlorination at −20°. On chromatography, a very small yield of a crystalline *hexachloride* was obtained which formed bunches of colourless needles, m. p. 119—120°, from light petroleum (b. p. 60—80°) (Found : C, 29·8; H, 3·3. $C_8H_{10}Cl_6$ requires C, 30·1; H, 3·2%).

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21-*Hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione*.

By George Cooley, Bernard Ellis, and Vladimir Petrow.

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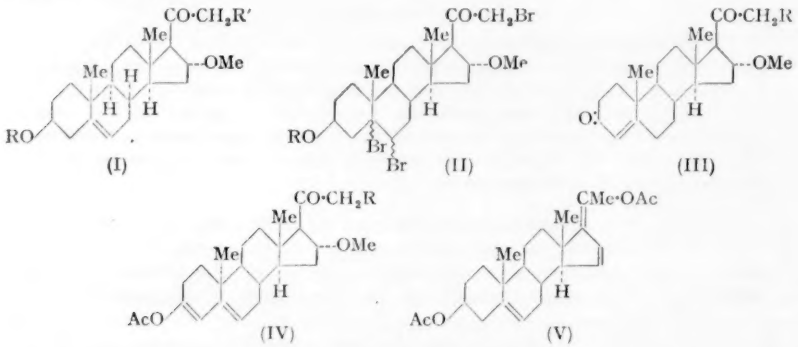
21-Hydroxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OH), required for study as a mineralocorticoid antagonist, has been prepared by bromination of 3β-hydroxy-16α-methoxypregn-5-en-20-one (I; R = R′ = H) at $C_{(21)}$, followed by acetolysis, Oppenauer oxidation at $C_{(3)}$ and hydrolysis of the resulting 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = Ac). 3β : 20-Diacetoxypregna-5 : 15 : 17-triene is prepared from 3β-acetoxypregna-5 : 16-dien-20-one.

Direct conversion of a pregnan-20-one into the 21-bromo-derivative is not generally possible owing to the superior mobility of the tertiary hydrogen atom at $C_{(17)}$. It seemed likely, however, that such bromination might occur in the 16α-methoxypregnan-20-one series in which the (+*I*) methoxyl group introduces a measure of deactivation at $C_{(17)}$. We therefore treated 3β-acetoxy-16α-methoxypregn-5-en-20-one (I; R = Ac; R′ = H) (Fukushima and Gallagher, *J. Amer. Chem. Soc.*, 1951, **73**, 196) in acetic acid first with one and then with a second equivalent of bromine, obtaining thereby a product from which crystalline material consisting essentially of a tribromide was isolated. The constitution of 3β-acetoxy-5 : 6 : 21-tribromo-16α-methoxypregnan-20-one (II; R = Ac) is assigned to this compound since on reaction at room temperature with sodium iodide in benzene–ethanol, followed by acetolysis of the intermediate 3β-acetoxy-21-iodo-16α-methoxypregn-5-en-20-one (I; R = Ac, R′ = I) with potassium acetate in boiling acetone, it was converted into 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one (I; R = R′ = Ac), also obtained in very low yield by the oxidation of (I; R = Ac, R′ = H) with lead tetra-acetate (cf. Ehrhart, Ruschig, and Anmüller, *Ber.*, 1939, **72**, 2035).

Extension of this reaction to 16α-methoxypregnenolone (I; R = R′ = H) (Gould, Gruen, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 2510) readily gave (III; R = OH) in excellent overall yield. Bromination of (I; R = R′ = H) in *ethereal* solution gave 5 : 6 : 21-tribromo-3β-hydroxy-16α-methoxypregnan-20-one (II; R = H), converted by sodium iodide into the 21-iodide (I; R = H, R′ = I) and thence into the 21-acetate (I; R = H, R′ = OAc) by acetolysis. Oppenauer oxidation of the last compound furnished 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OAc), smoothly converted into 21-hydroxy-16α-methoxypregn-4-ene-3 : 20-dione (III; R = OH) by hydrolysis with aqueous methanolic potassium hydrogen carbonate.

Attempted acetolysis of (III; R = OAc) to 16α : 21-diacetoxypregn-4-ene-3 : 20-dione employing acetic anhydride–toluene-*p*-sulphonic acid under the conditions of Huffman and Lott (*J. Biol. Chem.*, 1948, **172**, 789) gave a product which gave correct analyses for the required compound but proved to be the enol acetate of the starting material, as it passed into (III; R = Ac) on mild hydrolysis followed by acetylation. Its formulation as 20 : 21-diacetoxy-16α-methoxypregna-4 : 17(or 4 : 20)-dien-3-one was rendered unlikely by the observation that both (I; R = R′ = Ac) and (I; R = Ac, R′ = H) were recovered unchanged after heating with acetic anhydride–toluene-*p*-sulphonic acid for 30 minutes at 100°. We therefore assign it the alternative constitution 3 : 21-diacetoxy-16α-methoxypregna-3 : 5-dien-20-one (IV; R = Ac) and in support thereof find that cholest-4-en-3-one and 16α-methoxyprogesterone (III; R = H) pass smoothly into the corresponding 3-enol acetates under the same experimental conditions. *Inter alia* we find that prolonged acetolysis of (I; R = Ac, R′ = H) leads to loss of the elements of methanol with formation of a diacetoxypregnatriene, also obtained, together with an isomeric enol acetate, directly from 3β-acetoxypregna-5 : 16-dien-20-one. Conversion of the last compound into 3β : 20-diacetoxypregna-5 : 16 : 20-triene by *iso*propenyl acetate has been described by Moffett and Weisblat (*J. Amer. Chem. Soc.*, 1952, **74**, 2183). This material differs from either of our two products which are therefore regarded as *cis*- and *trans*-isomers (about positions 17 and 20) of 3β : 20-diacetoxypregna-5 : 15 : 17-triene (V), in analogy with the production of isomeric 3β : 20-diacetoxy*allo*pregn-17-enes (Marshall, Kritchevsky, Liebermann, and Gallagher, *ibid.*, 1948, **70**, 1837) and 3β : 20-diacetoxypregna-5 : 17-dienes (Fieser and Huang-Minlon, *ibid.*, 1949, **71**, 1840) from 3β-hydroxy-*allo*pregnan-20-one and -pregn-5-en-3-one, respectively.



Experimental

Ultra-violet absorption spectra were determined for *iso*propyl alcoholic solutions by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses Ltd. Optical rotation were determined in chloroform solutions in a 2-dm. tube.

3β-Acetoxy-5 : 6 : 21-tribromo-16α-methoxypregnan-20-one (II; R = Ac).—3β-Hydroxy-16α-methoxypregn-5-en-3-one acetate (11 g.) in acetic acid (150 ml.) was treated at room temperature with bromine (4·75 g.) in acetic acid (15 ml.), decolorisation being complete within 1 min. Thereafter, more bromine (4·75 g.) in acetic acid (15 ml.) was added, and when absorption was complete (1·5 hr.) the mixture was poured into water. The solids obtained were

washed, air-dried, and crystallised from chloroform–methanol, giving a product (11·2 g.), m. p. 148—152°. Thrice crystallised from the same solvent mixture, the *tribromo*-compound formed needles, m. p. 159—160° (decomp.), $[\alpha]_D^{20}$ −18·2° (*c*, 2·15) (Found: C, 44·1; H, 5·3. $C_{24}H_{35}O_4Br_3$ requires C, 45·95; H, 5·6%). Although the m. p. of the material remained unchanged on further recrystallisation, the low analytical figure for carbon suggests contamination with a more highly brominated substance.

3β : 21-*Diacetoxy*-16α-*methoxypregn*-5-*en*-20-*one* (I; R = R′ = Ac).—(*a*) The foregoing tribromide (8 g.) in benzene (80 ml.) was treated for 24 hr. at room temperature with sodium iodide (16 g.) in absolute ethanol (100 ml.). After dilution with water, the mixture was extracted with ether, and the extract washed with 3% aqueous sodium thiosulphate, then with water, and dried. The crystalline residue obtained on removal of the solvents *in vacuo* at ≯30° was heated for 12 hr. under reflux in acetone (100 ml.) containing freshly fused potassium acetate (15 g.). Precipitation with water gave a colourless solid (5·2 g.), m. p. 128—130°. Purified from acetone and then from aqueous methanol, 3β : 21-*diacetoxy*-16α-*methoxypregn*-5-*en*-20-*one* formed flat needles, m. p. 140—142°, $[\alpha]_D^{21}$ −20·6° (*c*, 2·25) (Found: C, 69·7; H, 8·7. $C_{26}H_{38}O_6$ requires C, 69·9; H, 8·4%).

In one experiment, the intermediate 3β-*acetoxy*-21-*iodo*-16α-*methoxypregn*-5-*en*-20-*one* was isolated as plates (from ethanol), m. p. 126°, $[\alpha]_D^{24}$ +40·6° (*c*, 0·48) (Found: C, 56·0; H, 6·45; I, 25·1. $C_{24}H_{35}O_4I$ requires C, 56·0; H, 6·85; I, 25·0%).

(*b*) (By Mrs. W. J. Adams.) 3β-Hydroxy-16α-methoxypregn-5-en-20-one acetate (900 mg.) in a saturated solution of lead tetra-acetate in acetic acid (41 ml.) containing a little acetic anhydride was kept for 17 hr. at 75—80°. The product, isolated with ether, was chromatographed on B.D.H. alumina (20 g.), elution with benzene giving unchanged acetate (350 mg.). Further elution with ether and ether–acetone (1 : 1) gave 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one (50 mg.), needles (from methanol), m. p. 139—140°, not depressed in admixture with a specimen prepared by method (*a*).

5 : 6 : 21-*Tribromo*-3β-*hydroxy*-16α-*methoxypregnan*-20-*one* (II; R = H).—Bromine (9·5 g.) in acetic acid (20 ml.) was added dropwise during 15 min. to a stirred suspension of 3β-hydroxy-16α-methoxypregn-5-en-3-one (10 g.) in ether (500 ml.), absorption being complete after a further 5 min. The solution was washed with water, aqueous sodium hydrogen carbonate, and water, and cooled to 0°. The crystalline product [6·7 g.; m. p. 140° (decomp.)] was removed and the mother-liquor concentrated to give a further quantity [5·5 g.; m. p. 135° (decomp.)] of less pure material. Recrystallised from ethyl acetate–light petroleum the *tribromide* formed prisms, m. p. 140—143° (decomp.), $[\alpha]_D^{22}$ +2·5° (*c*, 0·53) (Found: C, 45·7; H, 5·2. $C_{22}H_{33}O_3Br_3$ requires C, 45·2; H, 5·7%).

21-*Acetoxy*-3β-*hydroxy*-16α-*methoxypregn*-5-*en*-20-*one* (I; R = H, R′ = Ac).—The foregoing tribromide (30 g.), suspended in benzene (300 ml.), was treated for 24 hr. at room temperature with sodium iodide (60 g.) in absolute ethanol (350 ml.). The mixture was diluted with water and extracted with ether, and the extract washed with 3% aqueous sodium thiosulphate and then water. After being dried, the solvents were removed *in vacuo* at ≯30°. The crystalline residue was heated for 18 hr. under reflux in acetone (450 ml.) containing freshly fused potassium acetate (60 g.), and the product (17·2 g., m. p. 160—162°) obtained on the addition of water was purified from aqueous methanol. 21-*Acetoxy*-3β-*hydroxy*-16α-*methoxypregn*-5-*en*-20-*one* separated in flat needles, m. p. 164—166°, $[\alpha]_D^{24}$ −6·2° (*c*, 0·42) (Found: C, 71·0; H, 8·95. $C_{24}H_{36}O_5$ requires C, 71·25; H, 9·0%). Acetylation in pyridine gave 3β : 21-diacetoxy-16α-methoxypregn-5-en-20-one, m. p. and mixed m. p. 140—142°.

21-*Acetoxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* (III; R = Ac).—A solution of 21-acetoxy-3β-hydroxy-16α-methoxypregn-5-en-20-one (16·7 g.) in toluene (700 ml.) and *cyclo*hexanone (160 ml.) was distilled until 150 ml. of distillate had collected. After the addition of aluminium *iso*propoxide (8 g.) in toluene (35 ml.), the mixture was refluxed for 30 min., cooled somewhat, and treated with acetic acid (4 ml.) in toluene (25 ml.). The solvents were removed by steam-distillation and the solids obtained were collected and air-dried. These were extracted with hot ethyl acetate, and the extract was concentrated and treated with light petroleum to give a crystalline solid (10·2 g.; m. p. 155—156°). Recrystallised from acetone–hexane, 21-*acetoxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* formed prisms, m. p. 162—163°, $[\alpha]_D^{23}$ +116° (*c*, 0·47) (Found: C, 71·5; H, 8·5. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). Light absorption: $\lambda_{max.}$ 240 mμ (ε 16,800).

21-*Hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione* (III; R = OH).—The foregoing compound (1 g.) in methanol (100 ml.) was treated for 18 hr. at room temperature with potassium hydrogen carbonate (1 g.) in water (20 ml.). The product, isolated with ether after dilution of the reaction

mixture with brine, crystallised from acetone–hexane, to give 21-*hydroxy*-16α-*methoxypregn*-4-*ene*-3 : 20-*dione*, needles, m. p. 137—138°, $[\alpha]_D^{20}$ +105° (*c*, 1·2) (Found : C, 73·1; H, 8·6. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·9%). Acetylation in pyridine gave the 21-acetoxy-compound, m. p. and mixed m. p. 162—163°.

3 : 21-*Diacetoxy*-16α-*methoxypregna*-3 : 5-*dien*-20-*one* (IV; R = Ac).—21-Acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (1 g.) and toluene-*p*-sulphonic acid (500 mg.) were heated with acetic anhydride (50 ml.) for 30 min. at 100°. Crystallisation from aqueous methanol gave the *enol acetate* (60%), flat needles, m. p. 132—134·5°, $[\alpha]_D^{20}$ −64·5° (*c*, 1·62) (Found : C, 69·7, 70·4; H, 8·3, 8·0. $C_{26}H_{36}O_6$ requires C, 70·2; H, 8·2%). Light absorption : $\lambda_{max.}$ 235 mμ (ε 19,700).

The enol acetate (450 mg.) was hydrolysed at room temperature with potassium hydrogen carbonate (500 mg.) in aqueous methanol (60 ml. of 80%). After 48 hr., the product was isolated with ether and acetylated in pyridine, to give 21-acetoxy-16α-methoxypregn-4-ene-3 : 20-dione (50 mg.), prisms, m. p. and mixed m. p. 158—162° (from ethyl acetate–light petroleum).

16α-*Methoxyprogesterone*.—3β-Hydroxy-16α-methoxypregn-5-en-3-one (5 g.) and aluminium *iso*propoxide (8 g.) in toluene (120 ml.) and *cyclo*hexanone (40 ml.) were heated under reflux for 40 min. The mixture was washed with dilute sulphuric acid, then with water, and the solvents were removed by steam-distillation. The product on crystallisation from ethyl acetate–light petroleum gave 16α-methoxyprogesterone (70%) in needles, m. p. 131—132°, $[\alpha]_D^{20}$ +102° (Fukushima and Gallagher, *loc. cit.*, give m. p. 134—135·5°, $[\alpha]_D^{22}$ +106°).

3-*Acetoxy*-16α-*methoxypregna*-3 : 5-*dien*-20-*one* (50%), prepared by heating 16α-methoxyprogesterone (800 mg.) and toluene-*p*-sulphonic acid (400 mg.) in acetic anhydride (40 ml.) for 30 min. at 100°, formed plates (from aqueous methanol), m. p. 129—130°, $[\alpha]_D^{22}$ −84° (*c*, 1·1) (Found : C, 74·2; H, 8·8. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

3-Acetoxycholesta-3 : 5-diene (60%), prepared from cholest-4-en-3-one under conditions identical with those cited above, formed needles (from methanol), m. p. 79—80°, $[\alpha]_D^{20}$ −96° (Westphal, *Ber.*, 1937, **70**, 2128, gives m. p. 81°, $[\alpha]_D$ −100·4°).

Prolonged Action of Acetic Anhydride and Toluene-p-*sulphonic Acid on* 3β-*Acetoxy*-16α-*methoxypregn*-5-*en*-3-*one*.—A solution of the steroid (4·5 g.) and toluene-*p*-sulphonic acid (2·5 g.) in acetic anhydride (500 ml.) was gently boiled, the solvent being permitted to distil during 7 hr. The residual dark mixture (50 ml.) was treated with water, and the product isolated with ether. Light petroleum (50 ml.; b. p. 40—60°) was added to its solution in ether (50 ml.), a small precipitate of dark amorphous material was removed by filtration, and the filtrate was passed through a column (11 × 3·3 cm.) of acid-washed alumina. Elution with ether–light petroleum (1 : 1) gave a gummy solid (2·1 g.), which, purified from aqueous methanol, gave 3β : 20-*diacetoxypregna*-5 : 15 : 17-*triene* (*isomer A*), flat blades, m. p. 113—114°, $[\alpha]_D^{20}$ −155° (*c*, 1·02) (Found : C, 75·6; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·35; H, 8·6%). Light absorption : $\lambda_{max.}$ 242 mμ (ε 13,700). Hydrolysis with hot aqueous-methanolic potassium hydrogen carbonate converted it into 3β-hydroxypregna-5 : 16-dien-20-one, m. p. and mixed m. p. 212—214°, also obtained (as acetate) on one occasion when the enol acetate (isomer A) in methanol was warmed briefly with charcoal. The compound appeared to be unstable in the solid state, the m. p. falling to *ca.* 100° after six weeks.

Enol Acetylation of 3β-*Acetoxypregna*-5 : 16-*dien*-20-*one*.—A solution of 3β-acetoxypregna-5 : 16-dien-20-one (6 g.) and toluene-*p*-sulphonic acid (3 g.) in acetic anhydride (600 ml.) was gently boiled, the solvent being permitted to distil during 7 hr. The dark product, isolated with ether, was dissolved in ether–light petroleum (150 ml. of 1 : 1), and the solution filtered through a column (10 × 2·5 cm.) of acid-washed alumina. The yellowish solid (4·3 g.) obtained was fractionated from warm aqueous acetic acid, giving *isomer B* of 3β : 20-*diacetoxypregna*-5 : 15 : 17-*triene* (0·8 g.), long needles (from methanol), m. p. 167—168°, $[\alpha]_D^{22}$ −245° (*c*, 1·31) (Found : C, 75·1; H, 8·6. $C_{25}H_{34}O_4$ requires C, 75·35; H, 8·6%). Light absorption : $\lambda_{max.}$ 246 mμ (ε 17,100). 3β-Hydroxypregna-5 : 16-dien-20-one was obtained on hydrolysis of the enol acetate (isomer B) with hot aqueous-methanolic potassium hydrogen carbonate.

Careful dilution of the aqueous acetic acid mother-liquor gave isomer A (1 g.), blades (from aqueous methanol), m. p. 113—114°, not depressed in admixture with a specimen prepared as in the preceding experiment.

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Gladiolic Acid. Part V. Syntheses of Some Methoxybenzenetricarboxylic Acids.*

By D. Gardner, John Frederick Grove, and Doreen Ismay.

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The synthesis of 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid is described and some properties of the methoxybenzenetricarboxylic acids are compared.

The main product of the oxidation of gladiolic acid with boiling permanganate was shown by Grove (*Biochem. J.*, 1952, **50**, 648) to be 4-methoxybenzene-1 : 2 : 3 : 5-tetracarboxylic acid whose structure was proved by synthesis; a methoxybenzenetricarboxylic acid, substance C, which gave positive results in tests for an *o*-phthalic acid and was not, therefore, methoxytrimesic acid (Ullmann and Brittner, *Ber.*, 1909, **42**, 2539), was also formed in very low yield under certain conditions. In 1946, when this acid was first obtained, only 6-methoxybenzene-1 : 2 : 4-tricarboxylic acid (Posternak, *Helv. Chim. Acta*, 1940, **23**, 1046) of the five possible methoxytrimellitic and methoxyhemimellitic acids had been described. Accordingly the synthesis of the four remaining acids was commenced, by permanganate oxidation of the methyl ethers of appropriate hydroxyacetophenones obtained by Fries rearrangement of suitable dimethylphenyl acetates. While this work was in progress 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid was obtained by Wilds and Djerassi (*J. Amer. Chem. Soc.*, 1946, **68**, 1862), by a different route; and later, 4-methoxybenzene-1 : 2 : 3- and 5-methoxybenzene-1 : 2 : 4-tricarboxylic acid were described by Buehler, Spees, and Sanguinetti (*ibid.*, 1949, **71**, 11). None of these acids was identical with the acid obtained from gladiolic acid which must therefore be 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid, and this has now been confirmed by synthesis. Methylation of 2-hydroxy-3 : 4-dimethylacetophenone, prepared by Fries rearrangement at 130° of 2 : 3-dimethylphenyl acetate (von Auwers and Mauss, *Annalen*, 1928, **460**, 240), proved difficult, but was achieved by prolonged heating with methyl iodide and potassium carbonate in acetone. Oxidation with permanganate then gave the desired acid, identical with the gladiolic acid oxidation product.

When the Fries rearrangement of 2 : 3 dimethylphenyl acetate was carried out in nitrobenzene at 20°, the *p*-hydroxy-ketone, 4-hydroxy-2 : 3-dimethylacetophenone, was the sole product. von Auwers and his collaborators showed that 3 : 5-dimethylphenyl acetate gave an *o*-hydroxy-ketone while 2 : 5-dimethylphenyl acetate gave a *p*-hydroxy-ketone in the Fries rearrangement at 100°. These findings were confirmed in the present study; in addition it was observed that 3 : 5-dimethylphenyl acetate yielded the *o*-hydroxy-ketone and no *p*-hydroxy-ketone under mild conditions (nitrobenzene solution at 0°), whereas 2-hydroxy-3 : 6-dimethylacetophenone was not obtained from 2 : 5-dimethylphenyl acetate even under conditions sufficiently drastic to cause migration of the alkyl substituents.

Permanganate oxidation of 4-methoxy-2 : 3-dimethylacetophenone gave 4-methoxybenzene-1 : 2 : 3-tricarboxylic acid. 5-Methoxybenzene-1 : 2 : 4-tricarboxylic acid was obtained similarly from both 2-methoxy-4 : 5- and 4-methoxy-2 : 5-dimethylacetophenone; from the last compound the intermediate 2 : 5-dicarboxy-4-methoxyphenylglyoxylic acid was also isolated.

In the preparation of 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid essentially according to the method of Wild and Djerassi (*loc. cit.*), esterification during continuous extraction with ethyl acetate led to the isolation of the monoethyl ester, from which the acid was obtained by hydrolysis.

The trimethyl esters of the five methoxyhemimellitic and trimellitic acids were prepared and are to be preferred as reference compounds, in agreement with the views of earlier workers. The acids have characteristic infra-red spectra and can be identified by this means but their decomposition points vary with the rate of heating and in general are not

* Part IV, *J.*, 1953, 3646.

depressed on admixture with an acid of higher though similar decomposition point. The esters, on the other hand, depressed each other's melting points when these lay close together. Their infra-red spectra are also characteristic, and have been deposited with the Society.

Experimental

M. p.s are corrected. Some microanalyses are by Messrs. W. Brown and A. G. Olney. Infra-red spectra were determined by using the apparatus described in earlier papers (Duncanson, Grove, and Zealley, *J.*, **1331**, 1953).

Fries Rearrangement of 2 : 3-*Dimethylphenyl Acetate.*—(a) *At* 20°. Powdered anhydrous aluminium chloride (15 g., 1·8 mols.) was added in portions with stirring to 2 : 3-dimethylphenyl acetate (10·0 g.; b. p. 120°/15 mm.) (Smith and Opie, *J. Org. Chem.*, 1941, **6**, 427) in nitrobenzene (50 g.), at $< 20°$ (ice-cooling). After 48 hr. the mixture was poured over cracked ice and concentrated hydrochloric acid, ether was added, and after separation the ether–nitrobenzene layer was extracted with 2N-sodium hydroxide. Acidification of the alkaline extract, extraction with ether, and recovery furnished 4-*hydroxy*-2 : 3-*dimethylacetophenone*, colourless prisms (from ethanol), m. p. 145° (5·3 g.) (Found: C, 73·2; H, 7·3. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%). It was insoluble in light petroleum, and gave no colour with ferric chloride in ethanol. The *semicarbazone* formed prisms, m. p. 226° (decomp.), from ethanol (Found: N, 18·7. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

The 4-hydroxy-ketone (2·0 g.), methyl sulphate (2 g.), and 20% aqueous sodium hydroxide (6 ml.) were shaken vigorously. The resulting alkali-insoluble oil was extracted with ether, and treated with light petroleum, furnishing 4-*methoxy*-2 : 3-*dimethylacetophenone* (2·0 g.), plates, m. p. 33° [Found: C, 73·8; H, 7·8%; *M* (Rast), 168. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%; *M*, 178]. The *semicarbazone* formed prisms, m. p. 216° (decomp.), from ethanol (Found: N, 18·4. $C_{12}H_{17}O_2N_3$ requires N, 17·9%).

(b) *At* 130°. 2 : 3-Dimethylphenyl acetate (10 g.) and anhydrous aluminium chloride (15 g.) were heated 1 hr. at 130°, the complex was decomposed with ice and hydrochloric acid, and the oily product extracted with ether. Recovery followed by distillation *in vacuo* yielded 2-hydroxy-3 : 4-dimethylacetophenone, a yellow oil, b. p. 140°/12 mm. (6·2 g.) (Smith and Opie, *loc. cit.*). It was miscible with light petroleum, and gave an intense green colour with ferric chloride in ethanol, becoming violet on dilution with water.

2-*Methoxy*-3 : 4-*dimethylacetophenone.*—The 2-hydroxy-ketone (2·5 g.), methyl iodide (12 g.), and potassium carbonate (2·5 g.) in acetone (50 ml.) were heated under reflux for 6 days, further quantities of methyl iodide being added from time to time. After concentration and addition of water (50 ml.), the solution was extracted with ether. Removal of the organic solvents left an oil which was taken up again in ether and exhaustively extracted with aqueous sodium hydroxide (20%; 10 × 50 ml.). Unchanged 2-hydroxy-ketone (1·0 g.) was recovered from the alkaline extract. The neutral fraction on recovery furnished 2-*methoxy*-3 : 4-*dimethylacetophenone*, a colourless oil (0·8 g.), b. p. 104°/2 mm. ($>C{=}O$ absorption at 1690 cm.$^{-1}$) (Found: C, 74·1; H, 7·9%), characterised as its *semicarbazone*, plates (from ethanol), m. p. 196° (Found: C, 61·4; H, 7·1; N, 17·4; OMe, 13·5. $C_{12}H_{17}O_2N_3$ requires C, 61·25; H, 7·3; N, 17·9; OMe, 13·2%). The methoxyacetophenone gave no colour with ferric chloride.

3-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic Acid.*—Potassium permanganate (5% solution; 25 ml.) was added dropwise during 30 min. to a stirred suspension of 2-methoxy-3 : 4-dimethylacetophenone (0·4 g.) in sodium carbonate (10 ml.; saturated solution) at 60°. The reaction was continued under reflux for 6 hr. after the addition of a further 75 ml. of permanganate solution. Excess of permanganate was then destroyed by the addition of methanol, the manganese dioxide filtered off, and the filtrate acidified with concentrated hydrochloric acid. The oil obtained by 24 hours' continuous extraction with ethyl acetate and recovery was oxidised in 3N-sulphuric acid (10 ml.) with potassium permanganate (25 ml.; 5%) at 100°, excess of permanganate removed by the addition of sodium sulphite, and the acid solution extracted with ethyl acetate. After two crystallisations from a very small volume of water, or from acetone–benzene, the solid extract formed prisms (97 mg., 18%) of 3-*methoxybenzene*-1 : 2 : 4-*tricarboxylic acid*, (C.S. 102 *), m. p. 198—200° (decomp.) [Kofler block, very rapid heating, 209—210° (decomp.)]

* This and similar designations denote infra-red spectra which have been deposited with the Society. Photo-copies may be obtained, price 3*s.* 0*d.* each per copy, on application stating the C.S. no. to the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

[Found : C, 50·3, 49·9; H, 3·4, 3·7%; equiv. 78. $C_{10}H_8O_7$ requires C, 50·0; H, 3·4%; equiv., 80 (tribasic acid)].

The *trimethyl ester* (C.S. 103) formed in 24 hr. in methanol with excess of ethereal diazomethane crystallised from methanol in prisms, m. p. 75° (Found : C, 55·4; H, 5·1; OMe, 43·6. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0; 4OMe, 44·0%).

The *anhydride* formed by sublimation of the acid at 160—180°/10^{-1} mm. formed needles, m. p. 165—168° (Found : C, 54·1; H, 3·0. $C_{10}H_6O_6$ requires C, 54·1; H, 2·7%).

When the m. p. of the acid is taken on the Kofler block with a slow rate of heating it is found to be 165—168°, the m. p. of the anhydride. Thus the m. p. of the acid, 160—165°, originally recorded (Grove, *loc. cit.*) is actually that of the anhydride.

3-Methoxybenzene-1 : 2 : 4-tricarboxylic acid did not depress the m. p. of the methoxybenzenetricarboxylic acid obtained from gladiolic acid and the infra-red spectra were identical. The trimethyl esters of the two acids were also identical.

4-*Methoxybenzene*-1 : 2 : 3-*tricarboxylic Acid.*—4-Methoxy-2 : 3-dimethylacetophenone (0·35 g.) was oxidised with potassium permanganate, first in sodium carbonate and then in 3N-sulphuric acid as described for the preparation of 3-methoxybenzene-1 : 2 : 4-tricarboxylic acid. The acid (C.S. 104) obtained by ethyl acetate extraction crystallised from a little water in prisms (123 mg., 26%), m. p. 222° unchanged on cooling and reheating, or after 5 minutes' heating at 230° (Buehler *et al.*, *loc. cit.*, give m. p. 215—216°) (Found : C, 49·9; H, 3·5%). The trimethyl ester (C.S. 105) formed prisms, m. p. 92° (lit., 91—92°), from methanol. Sublimation of the acid at 200—210°/10^{-1} mm. gave the *anhydride*, prisms, m. p. 222° (Found : C, 54·0; H, 3·0%).

5-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic Acid.*—(*a*) 2-Methoxy-4 : 5-dimethylacetophenone (1·0 g., m. p. 56°) (von Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 162) was oxidised with potassium permanganate in sodium carbonate as described above. Crystallisation of the product from ethyl acetate gave the acid (C.S. 106), m. p. 222—223° (decomp.) (675 mg., 50%) (Buehler *et al.*, *loc. cit.*, give m. p. 224—225°) (Found : C, 49·7; H, 3·9%). The trimethyl ester (C.S. 107) crystallised from light petroleum in prisms, m. p. 62° (lit., 62·5—63°) (Found : C, 55·2; H, 5·1%).

(*b*) 4-Methoxy-2 : 5-dimethylacetophenone (1·0 g.; m. p. 78°) (von Auwers *et al.*, *loc. cit.*, 1926) was oxidised as in (*a*). Treatment of the gummy ethyl acetate extract with benzene furnished a solid which crystallised from water in prisms, m. p. 216—219° (decomp.) (780 mg., 52%), of 2 : 5-*dicarboxy*-4-*methoxyphenylglyoxylic acid* [Found : C, 49·2; H, 3·2%; equiv., 87. $C_{11}H_8O_8$ requires C, 49·2; H, 3·0%; equiv., 89 (tribasic acid)]. Oxidation of this acid (200 mg.) with permanganate in sulphuric acid in the usual way gave 5-methoxybenzene-1 : 2 : 4-tricarboxylic acid (125 mg.) (overall yield 36%).

5-*Methoxybenzene*-1 : 2 : 3-*tricarboxylic Acid.*—4-Methoxy-2 : 6-dimethylbenzaldehyde (0·5 g.; m. p. 50°) (Wilds and Djerassi, *loc. cit.*) was oxidised in sodium carbonate with potassium permanganate as described above. Continuous extraction of the acidified solution with ethyl acetate and crystallisation of the solid product from water gave the *monoethyl ester* of the desired acid as needles, m. p. 177—178° (decomp.) [Kofler block, m. p. 185—187° (decomp.)] (Found : C, 54·0; H, 4·8. $C_{12}H_{12}O_7$ requires C, 53·7; H, 4·5%). Methylation with ethereal diazomethane in methanol yielded an ethyl dimethyl ester, prisms (from methanol), m. p. 96° [Found : C, 56·5; H, 5·6; OAlk (as OMe), 41·2. Calc. for $C_{14}H_{16}O_7$: C, 56·7; H, 5·4; OAlk (as OMe), 41·9%]. Wilds and Djerassi described an ethyl dimethyl ester, m. p. 98—99°. Hydrolysis of the ethyl ester with methanolic potassium hydroxide and treatment of the salt obtained with hydrochloric acid as described by Wilds and Djerassi gave 5-methoxybenzene-1 : 2 : 3-tricarboxylic acid (C.S. 108), m. p. 211—212° (decomp.) (lit., 211—212°) (420 mg., 57%) (Found : C, 49·9; H, 3·6%). Sublimation at 200°/10^{-1} mm. gave the *anhydride*, m. p. 198° (Found : C, 53·7; H, 3·2%). The trimethyl ester (C.S. 109), prisms, m. p. 85° (lit., 83—83·5°), was obtained by methylation of the acid in methanol with excess of ethereal diazomethane.

6-*Methoxybenzene*-1 : 2 : 4-*tricarboxylic acid* (C.S. 110), m. p. 258° (decomp.), was prepared according to Posternak (*loc. cit.*) [Posternak gives m. p. 251° (decomp.)]. The trimethyl ester (C.S. 111) formed prisms (cf. Berner, *J.*, 1946, 1052), m. p. 145° (lit., 144°) (Found : C, 55·5; H, 5·2; OMe, 43·0%).

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The Synthesis of δ-Succinamidolævulic Acid and Related Compounds.

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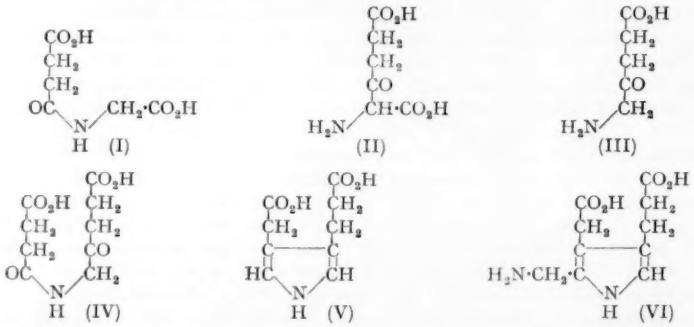
δ-Chloro- and δ-*N*-substituted derivatives of lævulic acid have been prepared. The conversion of succinimido-compounds into the corresponding *N*-substituted succinamic acids has been studied.

Succinamido[α-^{14}C]acetic acid, δ-[^{15}N]aminolævulic acid hydrochloride, and δ-succinamidolævulic acid have been synthesised in order to study their possible rôles in porphyrin biosynthesis.

PREVIOUS work on the biosynthesis of protoporphyrin has shown that, for each molecule formed, eight molecules of glycine and eight molecules of a compound derivable from α-oxoglutarate are required (Wittenberg and Shemin, *J. Biol. Chem.*, 1950, **185**, 103; Muir and Neuberger, *Biochem. J.*, 1950, **47**, 97). On the basis of work with isotopically labelled acetate and succinate, Shemin and Kumin (*J. Biol. Chem.*, 1952, **198**, 827) postulated an asymmetric derivative of succinic acid as the compound which condenses initially with glycine; they also suggested that succinyl-coenzyme A might be the required "active" succinate. For many years it has been considered likely that the first tetrapyrrole formed is uroporphyrin. Each pyrrole ring in this compound carries carboxyl-bearing side chains in the two β-positions, and Neuberger, Muir, and Gray, (*Nature*, 1950, **165**, 948) suggested a mechanism of porphyrin biosynthesis, according with the isotope data then available, by which the first pyrrolic compound formed was such a dicarboxylic pyrrole (V) with free α-positions. It was assumed in this theory that the methene-bridge carbon atoms (derivable from the α-carbon atom of glycine) were condensed with the free α-positions at a later stage in order to account for the occurrence only of series I and III porphyrins in Nature, with the latter predominant.

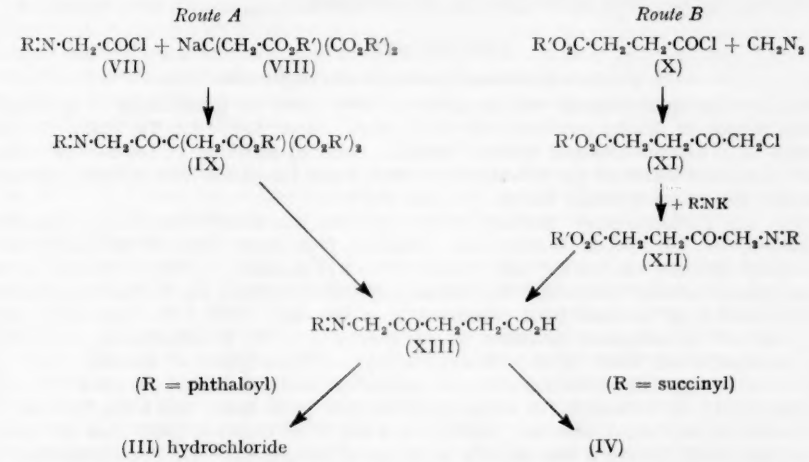
Accordingly, we set out in 1952 to synthesise a number of compounds formally derivable from glycine condensed with one or two molecules of succinic acid. By *N*-succinylation succinamidoacetic acid (I), and by α-*C*-succinylation α-amino-β-oxoadipic acid (II) would be formed. The latter compound would be expected to lose the glycine carboxyl group readily to give δ-aminolævulic acid (III). By addition of a second molecule of succinic acid, (I) or (III) could be converted into δ-succinamidolævulic acid (IV). This compound, by a reductive



self-condensation, might then form the pyrrole (V). Alternatively, a different pyrrole (VI) having the structure assigned to porphobilinogen by Cookson, Rimington, and Kennard (*Nature*, 1953, **171**, 875), might arise from a Knorr-type condensation of two molecules of (III). The aminomethyl α-substituent (which has arisen from glycine) would then be expected to give rise to the methene carbon atoms of the resulting uroporphyrin. It was thus desirable to be able to prepare (I), (III), and (IV) labelled either with ^{15}N or with ^{14}C at any position in the molecule, but especially in the position corresponding to the α-carbon atom of glycine, *viz.*, succinamido[α-^{14}C]acetic acid and [δ-^{14}C]lævulic acid derivatives.

A brief summary of the syntheses described below has been given in a preliminary communication (Neuberger and Scott, *Nature*, 1953, **172**, 1093). Only one of these compounds, (III), turned out to be a precursor (Shemin and Russell, *J. Amer. Chem. Soc.*, 1953, **75**, 4873; Neuberger and Scott, *loc. cit.*) and an outline of syntheses of labelled (III) was also given by Shemin and Russell. The synthesis of *labelled* (IV) was never eventually undertaken, since it was eliminated as a possible precursor by use of a test procedure not requiring isotopic labelling (Neuberger and Scott, *loc. cit.*), but succinamido[α-^{14}C]acetic acid and [^{15}N]aminolævulic acid hydrochloride were prepared.

Uniquely δ-substituted derivatives of lævulic acid are almost unknown. Windaus *et al.* (*Ber.*, 1921, **54**, 2745) prepared δ-benzamidolævulic acid by a Bamberger fission of ethyl β-4(5)-glyoxalylpropionate; Wynn and Corwin (*J. Org. Chem.*, 1950, **15**, 203) prepared the hydrochloride of (III) in low yield by reduction of methyl δ-hydroxyiminoacetylacrylate. As far as we are aware no other δ-substituted derivatives have been described; the βδ-dihalogeno-derivatives are of course well known. It was at once apparent that a Dakin and West reaction between glycine and succinic anhydride might lead directly to (IV). This was attempted under a variety of conditions, but no crystalline material could be isolated, nor was there any evidence that the reaction had proceeded in the desired direction. Considering first (III) and (IV), two main lines of approach were then explored; these are set out schematically below.



By route A, an imidoacetyl chloride (VII) was condensed with an appropriate malonic ester derivative (VIII), followed by removal of the ester groups and decarboxylation, to give the δ-imidolævulic acid (XIII); an imido[α-^{14}C]acetyl chloride would thereby yield a [δ-^{14}C]lævulate. The imide ring would then either be opened with alkali (XIII; R = succinyl) to give (IV), or else be completely hydrolysed to the hydrochloride of (III). It is known that the ester groups of acylalkylmalonates cannot in general be removed by hydrolysis without splitting the whole molecule in such a way as to reverse the condensation (Bowman, *J.*, 1950, 325; Fonken and Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 831). Following therefore Bowman's method (*loc. cit.*), benzyl sodioethane-1 : 1 : 2-tricarboxylate (VIII; R′ = CH_2Ph) was condensed with phthaloyl- or succinyl-glycyl chloride. On catalytic reductive de-esterification and decarboxylation a low yield (34%) of the phthalimido-compound (XIII; R = phthaloyl) was obtained. With the succinimido-derivative (IX; R = succinyl) uptake of hydrogen was low, and a crystalline compound could not be isolated, nor was an alternative method (Bowman and Fordham, *J.*, 1952, 3945) employing 2 : 3-dihydropyran (VIII; R′ = tetrahydropyran-2-yl) more fruitful.

Route B was preferred for preparation of both (III) and (IV). Methyl δ-chlorolævulate

(XI; R′ = Me) was characterised by hydrolysis to the free acid and by conversion into thiazole derivatives. The melting points of these compounds, particularly that of the free base, did not agree with those reported by Ziegler (*J. Amer. Chem. Soc.*, 1944, **66**, 744). His synthesis was therefore repeated, giving products whose properties, including the *X*-ray diffraction pattern, agreed with those of the thiazoles prepared from (XI). The α-chloro-ketone (XI) was condensed with potassium phthalimide or succinimide in anhydrous dimethylformamide (cf. Sheehan and Bolhofer, *ibid.*, 1950, **72**, 2786). We found (at least with α-halogeno-ketones) that anhydrous potassium carbonate and succinimide may be used in this condensation, in place of the less available anhydrous potassium succinimide, without loss in yield (cf. Ing and Manske, *J.*, 1926, 2348). The succinimide ring opens readily on addition of alkali, as was shown by plotting pH change against time after addition of sodium hydroxide to the ester (XII; R = succinyl, R′ = Me). The free acid (IV) was isolated crystalline after treatment of a solution of the disodium salt with an acidic ion-exchange resin. It is necessary to hydrolyse the ester first with cold hydrochloric acid, since the ketonic ester (XII) is unstable to excess of alkali. However, when this procedure was applied to methyl succinimidoacetate, acid hydrolysis of the ester was found to proceed much less readily, and attempts to isolate the free acid (I) after treatment with sodium hydroxide gave a clear " glass " which appeared to be a loosely bound polymer of glycine and succinic acid. By treating succinimidoacetic acid with baryta and removal of the latter as the sulphate, crystalline (I) was obtained.

Experimental

M. p.s were determined with a Kofler apparatus.

Anhydrous dimethylformamide was prepared in 80% yield by formylation of dimethylamine with chloral (cf. Blicke and Chi-Jung Lu, *J. Amer. Chem. Soc.*, 1952, **74**, 3933). It was fractionated in a vacuum-jacketed Widmer column, material distilling at 153·5—154° being collected. Traces of water in the dimethylformamide lower the yields from Gabriel condensations in this solvent (cf. Cox and Warne, *J.*, 1951, 1896).

Succinyl- and Phthaloyl-glycyl Chlorides (VII).—Glycine was fused with succinic (Scheiber and Reckleben, *Ber.*, 1913, **46**, 2412) or phthalic (Drechsel, *J. pr. Chem.*, 1883, **27**, 418) anhydride, and the cooled product was treated with excess of thionyl chloride. After distillation of the unchanged thionyl chloride with added dry toluene at reduced pressure, the imidoacetyl chloride was recrystallised from benzene–light petroleum (b. p. 60—80°); (VII; R = succinyl), yield 60%, m. p. 79—81° (Scheiber and Reckleben, *loc. cit.*, give 76°); (VII; R = phthaloyl), yield 90%.

δ-Phthalimidolævulic Acid (XIII; R = phthaloyl).—Phthaloylglycyl chloride (44·7 g., 0·2 mole) was brought into reaction with the sodio-derivative of benzyl ethane-1 : 1 : 2-tricarboxylate (VIII; R′ = benzyl) (Bowman, *J.*, 1950, 325) (0·22 mole), this being followed by debenzylation in dry ethyl acetate. After two changes of catalyst (palladised strontium carbonate) uptake of hydrogen was slightly in excess of theoretical. On decarboxylation in boiling toluene and removal of the solvent in an oil-bath, a pale yellow viscous material remained. After 3 weeks, crystallisation commenced and on working up the material by Bowman's procedure 18 g. (34%) of crude product were obtained. Recrystallised from ethyl acetate, twice from water, and twice from benzene, *δ-phthalimidolævulic acid* melted at 158·5° (Found: C, 60·0; H, 4·4; N, 5·1. $C_{13}H_{11}O_5N$ requires C, 59·77; H, 4·25; N, 5·4%). A small quantity of the compound was esterified with ethanol–hydrogen chloride, and the resulting *ethyl δ-phthalimidolævulate*, recrystallised from hot (80°) water, had m. p. 79° (Found: C, 62·2; H, 5·35; N, 4·8. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·85%).

β-*Methoxycarbonylpropionyl Chloride* (X; R′ = Me).—Succinic anhydride (100 g., 1 mole) was refluxed with excess (95 c.c.) of dry methanol, heating being continued for 3·5 hr. after a clear solution had been obtained. On removal of the excess of methanol *in vacuo*, crystalline methyl hydrogen succinate was obtained in theoretical yield (cf. Riegel and Lilienfeld, *J. Amer. Chem. Soc.*, 1945, **67**, 1273). After recrystallisation from benzene–*cyclo*hexane, the half-ester (132 g., 1 mole) was treated with excess of thionyl chloride (93 c.c.) and set aside for 18 hr. The mixture was then warmed to 45° for 2 hr., 100 c.c. of dry toluene were added, and the excess of thionyl chloride and toluene removed *in vacuo* at 50°. On fractional distillation (10 cm. Vigreux column) the ester-chloride distilled at 63—65°/3 mm. (131 g., 87%).

Methyl δ-Chlorolævulate (XI; R′ = Me).—To a solution of diazomethane (0·76 mole) in dry ether (1270 c.c.), cooled to below −5°, was added with mechanical stirring a solution of the fore-

going chloride (56 g., 0·37 mole) in ether (200 c.c.) during 2 hr. The mixture was allowed to warm to room temperature overnight. The diazo-ketone had then partly separated as an oil which disappeared on addition of chloroform (200 c.c.). A small amount of fluffy precipitate was removed by filtration into a 2-l. three-necked flask. This was fitted with a reflux condenser, mechanical stirrer, and gas bubbling tube. Dry hydrogen chloride was passed in, resulting in a brisk evolution of nitrogen, and refluxing of the ether; passage of gas was continued for 1·5 hr. after visible evolution of nitrogen had ceased. The solution was left for 48 hr. at 5°, then concentrated to about 400 c.c. *in vacuo* from a bath at room temperature. It was then washed with water (3 × 100 c.c.) to remove the hydrogen chloride, and the combined water washings were extracted with ether (6 × 100 c.c.), since the ketone ester is quite soluble in water. The combined ether extracts were dried ($MgSO_4$) and the solvent was removed. The residual material distilled at 92—94°/2—3 mm., 79—80°/1 mm. (12-cm. Vigreux column), yielding 34·7 g. (57% based on the acid chloride) of pure *methyl δ-chlorolævulate* (Found: C, 43·9; H, 5·5; Cl, 21·7. $C_6H_9O_3Cl$ requires C, 43·8; H, 5·5; Cl, 21·5%).

Ethyl δ-chlorolævulate (XI; R′ = Et), prepared in a similar way, had b. p. 106—112°/1—2 mm.

The methyl ester (2·2 g.) was added to 6 c.c. of 7N-hydrochloric acid; solution took place almost immediately. The mixture was left for 28 hr. at 18° and taken to dryness *in vacuo*. The residue was left overnight *in vacuo* over potassium hydroxide, and then crystallised twice from dry ether–light petroleum (b. p. 60—80°), giving plates of the free *acid*, m. p. 72—73° (Found: C, 40·2; H, 4·75; Cl, 24·1. $C_5H_7O_3Cl$ requires C, 39·9; H, 4·7; Cl, 23·5%).

3-*Aminothiazole Derivatives.*—Methyl δ-chlorolævulate (1·45 g.) was dissolved in 1 c.c. of ethanol; thiourea (0·8 g.) in water (1 c.c.) was added, and the mixture shaken for 1 hr. The solution became warm and deposited crystals of the thiazole ester hydrochloride. On addition of ammonia solution (*d* 0·88; 1·2 c.c.) the crystals dissolved, but those of the free base appeared on cooling. After two crystallisations from 50% methanol, *methyl* β-3-*amino*-4(5)-*thiazolylpropionate* melted at 94—96° (Found: C, 45·3; H, 5·2; N, 15·3; S, 17·1. $C_7H_{10}O_2N_2S$ requires C, 45·15; H, 5·4; N, 15·05; S, 17·2%). The amino-ester was treated with 20% hydrochloric acid on a boiling-water bath. The crystals of β-3-amino-4(5)-thiazolylpropionic acid hydrochloride which formed on cooling were filtered off and recrystallised from 2N-hydrochloric acid; they had m. p. 244—246° (decomp.), with some darkening at 241° (Ziegler, *loc. cit.*, gives m. p. 243—244°) (Found: C, 34·4; H, 4·1; N, 12·85. Calc. for $C_6H_8O_2N_2S,HCl$: C, 34·5; H, 4·35; N, 13·4%). The hydrochloride (0·63 g.) was suspended in water (5 c.c.), and dilute aqueous ammonia was added until the solution was just alkaline to litmus, then one drop of dilute hydrochloric acid was added (pH = 5). The solution was concentrated, and the free base filtered off. After recrystallisation from water to constant m. p., β-3-amino-4(5)-thiazolylpropionic acid had m. p. 195—196°. A sample prepared by Ziegler's method had m. p. 195—197°, mixed m. p. 195° (Ziegler, *loc. cit.*, gives m. p. 213—214°). Comparison of the *X*-ray diffraction pattern of crystals of the free base (m. p. 196°) prepared by these two routes showed the following interplanar spacings, in order of decreasing intensity: 3·38, 4·85, 6·37 (from the chloro-ketone); 3·38, 4·87, 6·24 (Ziegler's route). It was concluded that the two substances were identical.

Methyl δ-[^{15}N]*Phthalimidolævulate* (XII; R = phthaloyl, R′ = Me).—Potassium phthalimide (30·7 atoms % excess ^{15}N; 10·35 g., 0·0555 mole) was dissolved in 50 c.c. of anhydrous dimethylformamide; to this was added methyl δ-chlorolævulate (9·137 g., 0·0555 mole) which was washed in with 5 c.c. of dimethylformamide. The mixture was shaken for ½ hr., then warmed at 60° for an hour. After isolation (cf. Sheehan and Bolhofer, *loc. cit.*) and recrystallisation from boiling water (2 l.), needles of *methyl* δ-[^{15}N]*phthalimidolævulate* had m. p. 96—97° (9·6 g.); a further 1·2 g. (m. p. 96—97°) were obtained on evaporation of the mother-liquor to 250 c.c., and treatment with charcoal; the total yield was 70·5% (this rather low yield may have been due to traces of moisture in the potassium [^{15}N]phthalimide; with non-isotopic material yields were generally over 80%) (Found: C, 61·0; H, 4·9; N, 4·9. $C_{14}H_{13}O_5N$ requires C, 61·1; H, 4·8; N, 5·1%). Ethyl δ-phthalimidolævulate was prepared similarly (80% yield); after two crystallisations from hot (80°) water, it had m. p. 79°, undepressed on admixture with the same compound prepared by route A.

Methyl δ-Succinimidolævulate (XII; R = succinyl, R′ = Me).—Powdered succinimide (9·9 g., 0·10 mole) was suspended in dimethylformamide (25 c.c.); on gentle warming, most of the solid went into solution. To this was added methyl δ-chlorolævulate (16·456 g., 0·10 mole), washed in with solvent. Anhydrous potassium carbonate (13·82 g., 0·10 mole) was added (in small portions to minimise the possibility of ring-opening by excess of carbonate) from a

stoppered weighing bottle, the mixture being shaken after each addition. When most of the carbonate had been added, heat was evolved (a transitory orange colour may develop, depending mainly on the purity of the succinimide). The last of the carbonate was washed in, and the flask stoppered and left overnight, reaction being completed by warming to 60° for 1 hr. Sheehan and Bolhofer's procedure (*loc. cit.*), designed for the isolation of phthalimido-compounds, was followed except that in place of the alkali wash the organic layer was washed twice with 5% sodium hydrogen carbonate; these washings were then extracted twice with chloroform. On evaporation of the dried chloroform extracts at reduced pressure (14 mm.) on a water-bath at 90° (a temperature high enough to remove residual dimethylformamide, but not sufficient to cause loss of succinimido-ester), the contents of the flask solidified spontaneously on cooling; the yield of crude product was 88% (85—90% when anhydrous potassium succinimide was used); the pale brown crystals had m. p. 61—62°. The crude solid was recrystallised twice from ether–light petroleum (b. p. 40—60°) (the hot solution required to be well seeded by adding a suspension of crystals in light petroleum), giving needles of *methyl δ-succinimidolævulate*, m. p. 75·5° (Found: C, 53·1; H, 5·8; N, 6·1. $C_{10}H_{13}O_5N$ requires C, 52·85; H, 5·8; N, 6·2%). The compound is remarkably soluble in cold water. Light absorption ($\lambda_{max.}$ 2675—2685 Å; $\varepsilon_{max.}$ 35·6) in aqueous solution is of the order expected from the ketone carbonyl group (cf. Braude, *Ann. Reports*, 1945, **42**, 112). By following the change of pH potentiometrically, on adding one equiv. of sodium hydroxide to a 0·1M-solution, it was found that opening of the imide ring was virtually complete after 1 hr. at 20°. From this solution a crystalline compound, presumably the sodium salt of methyl δ-succinamidolævulate, was the sole product. If two equivalents of alkali were added, after a few hours a brown " oil " separated on evaporation of most of the water at room temperature, and the reducing properties of the ketone were lost.

δ-Succinimidolævulic Acid (XIII; R = succinyl).—Methyl δ-succinimidolævulate (11·358 g., 0·05 mole) was dissolved in 7N-hydrochloric acid (25 c.c.) and left at room temperature for 7 days, by which time a faint brown colour had appeared. The mixture was then warmed to 40° and treated with charcoal, filtered, and left at 0° for 2 days, yielding needles, m. p. 125—128°. Mineral acid was removed by distillation at reduced pressure (10 mm.) from a bath at 30°; the yield of crude product was theoretical. Recrystallisation twice from chloroform–*cyclo*hexane gave *δ-succinimidolævulic acid* as stellate clusters of needles (9·8 g., 92%), m. p. 129° (Found: C, 50·8; H, 5·4; N, 6·3. $C_9H_{11}O_5N$ requires C, 50·7; H, 5·2; N, 6·6%).

δ-Succinamidolævulic Acid (IV).—δ-Succinimidolævulic acid (8·527 g., 0·04001 mole) was weighed into a 50-c.c. Emich filter beaker fitted with a grade-3 sintered filter. Water (10 c.c.) was added, followed by 20 c.c. of 2N-sodium hydroxide from a burette; a pink colour developed until most of the acid was in solution, whereupon the colour faded. A further 20 c.c. of alkali were added slowly (total 0·0800 mole), whereupon a marked yellow colour developed. Two hours after addition of the alkali, the mixture was warmed for 5 min. on a bath at 40°, then Zeokarb 225 (14 g.) was added. The mixture was left at 20° for 4 hr. with occasional shaking and then filtered, treated with charcoal at 40° for 15 min., and refiltered, and the acid allowed to crystallise as water was slowly removed in a vacuum-desiccator, giving a quantitative yield of crude product, m. p. 180—190°. Fractional crystallisation from water gave rectangular white plates of *δ-succinamidolævulic acid*: 6·2 g., m. p. 197—199°; 2·4 g., m. p. 185—190°; total yield 92% (Found: C, 46·6; H, 5·8; N, 6·2. $C_9H_{13}O_6N$ requires C, 46·8; H, 5·7; N, 6·1%). The disodium salt of the acid becomes yellow on melting and loses water; a solution of the melt in methanol gives an immediate intense violet colour in the cold with Ehrlich's reagent, with an absorption band at 553 mμ. When kept at the m. p. until effervescence has ceased, the material darkens and crystals appear which char above 260° without melting. This change may indicate formation of a pyrrole and is being investigated further.

δ-[^{15}N]Aminolævulic Acid Hydrochloride (III).—By refluxing (IV), (XII), or (XIII) for 8 hr. with 7N-hydrochloric acid (10 c.c./g. of imide), the amino-acid hydrochloride could be prepared in theoretical yield. The ^{15}N-labelled amino-acid was prepared by hydrolysis of methyl δ-[^{15}N]-phthalimidolævulate. On cooling, phthalic acid crystallised and was filtered off; after removal of the solvent by distillation *in vacuo*, the residue was recrystallised from dry methanol–ethyl acetate; it then had m. p. 145° (decomp.) (Wynn and Corwin, *loc. cit.*, give m. p. 144—147°). Light absorption: $\lambda_{max.}$ 2665 Å; $\varepsilon_{max.}$ 23·0, in water; after addition of 2 equiv. of sodium hydroxide and exposure to the air: $\lambda_{max.}$ 2760, $\varepsilon_{max.}$ 2000, in accordance with the expected formation at alkaline pH of a 2 : 5-disubstituted pyrazine (Hartley and Dobbie, *J.*, 1900, **77**, 846, give $\lambda_{max.}$ 2710 for 2 : 5-dimethylpyrazine); this solution was pale yellow and gave no colour with Ehrlich's reagent.

Methyl Succinimidoacetate.—Methyl bromoacetate (21·4 g., 0·14 mole) was treated with

succinimide (14·5 g., 0·144 mole) and potassium carbonate (20·0 g., 0·145 mole) in dimethylformamide (25 c.c.) by the procedure described. The resulting compound (19·2 g., 80%, m. p. 85—90°) was recrystallised from dry ether–light petroleum (b. p. 60—80°), giving needles of *methyl succinimidoacetate*, m. p. 96—97° (subl.) (Found: C, 49·0; H, 5·4; N, 8·1. $C_7H_9O_4N$ requires C, 49·1; H, 5·3; N, 8·2%). The ester is readily soluble in cold water.

Succinamidoacetic Acid (I).—Methyl succinimidoacetate (10·43 g., 0·061 mole) was dissolved in 7N-hydrochloric acid (100 c.c.) and left at 37° for 3 days (hydrolysis by hydrochloric acid was incomplete after a week at 20°, in contrast to the corresponding lævulate). The solution was taken to dryness *in vacuo* in a bath at 40°, and the flask left in a high vacuum over sodium hydroxide for 2 days. The resulting succinylglycine was dissolved in about 500 c.c. of boiling dry benzene; on cooling, transparent hexagonal plates separated, m. p. 115° (Scheiber and Reckleben, *loc. cit.*, give 113°). On working up the mother-liquors, the total yield was 8·61 g., 90%. This acid was dissolved in a little water and 1·95 equiv. of baryta were added during 2 hr.; after 1 hr. the mixture was heated to 70° on a water-bath. After cooling, the barium ions were precipitated with sulphuric acid, and most of the sulphate removed by centrifuging. The solution was now taken to dryness *in vacuo* on a bath at 50°. After desiccation, the white residue was extracted several times with boiling dioxan. The solution was filtered hot, and boiling *cyclo*hexane added, giving rectangular plates of *succinamidoacetic acid* (58%), m. p. 146° after a second recrystallisation (Found: C, 41·3; H, 4·9; N, 7·9. $C_6H_9O_5N$ requires C, 41·2; H, 5·2; N, 8·0%). Succinamido[α-^{14}C]acetic acid was prepared by this method, starting with bromo[α-^{14}C]acetic acid (0·10 mole), recrystallised from dry light petroleum (b. p. 60—80°); the bromoacetic acid was esterified with diazomethane; the overall yield was 40%.

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12-*Oxygenated Pregnane Derivatives. Part I.* (a) 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione*; (b) 12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione*; (c) 3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one*; *and* (d) *Miscellaneous Observations.*

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Degradation of deoxycholic acid to 3α : 12α-diacetoxypregnan-20-one (I) and conversion of the latter into the compounds named in the title are described. Some miscellaneous observations pertaining to the chemistry of these transformations are included.

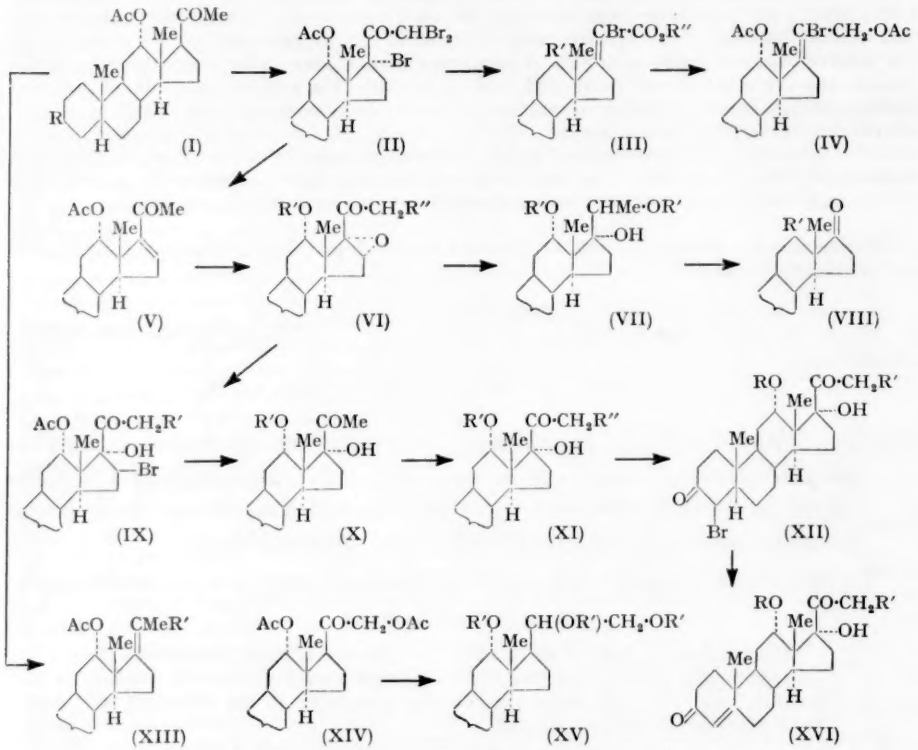
THE preparation of 12α : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (XVI; R = H, R′ = OH) has been undertaken, as this isomer of hydrocortisone is worthy of biological study.

Conversion of deoxycholic acid into 3α : 12α-diacetoxypregnan-20-one (I) was effected by adaptation of standard methods (Meystre, Frey, Wettstein, and Miescher, *Helv. Chim. Acta*, 1944, **27**, 1815; Meystre, Ehrmann, Neher, and Miescher, *ibid.*, 1945, **28**, 1252; Kendall, U.S.P. 2,541,074).

The preparation of 3α : 12α-diacetoxypregn-16-en-20-one (V) from (I) by allylic bromination of 3α : 12α : 20-triacetoxypregn-17-ene (XIII; R′ = OAc) (Marshall, Kritchevsky, Lieberman, and Gallagher, *J. Amer. Chem. Soc.*, 1948, **70**, 1837) as described by Djerassi and Scholz (*J. Org. Chem.*, 1949, **14**, 660) was uneconomic as only 20—25% overall yields were obtained. A more satisfactory procedure was bromination of (I) to the 17 : 21 : 21-tribromo-derivative (II), followed by reaction with sodium iodide in acetic acid. The high

overall yields referred to by Julian (118th Meeting Amer. Chem. Soc., Sept. 3—8, 1950, p. 19c) were, however, reached only with 25-g. batches, falling to *ca.* 50% with larger quantities.

(a) *Preparation of* 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = H, R′ = OAc).—Epoxidation of (V) with alkaline hydrogen peroxide (Julian, Meyer, Karpel, and Waller, *J. Amer. Chem. Soc.*, 1950, **72**, 5154) furnished the 16α : 17α-epoxide (VI; R′ = Ac, R″ = H) in good yield, the constitution of which was confirmed by reduction with lithium aluminium hydride or sodium borohydride to a tetraol formulated as (VII; R = α-OH, R′ = H) on the basis of molecular rotations [see (d) (viii)]. The compound gave the 3α : 12α : 20β-triacetate (VII; R′ = Ac) on acetylation and testane-3 : 12 : 17-trione (VIII; R = R′ = :O) on cautious oxidation with chromic acid.



Throughout the text, R = α-OAc unless otherwise stated.

No difficulty was experienced in cleaving the epoxide ring with hydrogen bromide, to give 3α : 12α-diacetoxy-16β-bromo-17α-hydroxypregnan-20-one (IX; R′ = H) which was also prepared from (V) in one operation by reaction with *N*-bromoacetamide in aqueous acidic *tert.*-butanol (cf. Sarett, *J. Biol. Chem.*, 1946, **162**, 628). Debromination of (IX) by Raney nickel in ethanol, as recommended by Julian *et al.* (*loc. cit.*), gave erratic yields, but by using hydrogen and 2% palladium–calcium carbonate (Busch and Stove, *Ber.*, 1916, **49**, 1063), consistent yields of (X; R′ = Ac) exceeding 90% were readily obtained [cf. (d) (v)].

The 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one prepared in this way formed needles which usually melted at 74—77° and occasionally at 104—105°. In addition to this unexpectedly low melting point, the infra-red spectrum of the material * showed

* Kindly determined by Dr. A. E. Kellie, Courtauld Institute of Biochemistry, who will report elsewhere results on this and other compounds herein described.

certain unusual features. We studied its reactions in some detail in order to establish its structure. The compound was largely unchanged on attempted acetylation, although small quantities of a new product which was probably 3α : 12α : 17α-triacetoxypregnan-20-one were also formed. It was unaffected by *N*-bromosuccinimide, lead tetra-acetate, and hydrogen bromide. Careful oxidation with chromium trioxide at room temperature led to 3α : 12α-diacetoxytestan-17-one (VIII; R′ = α-OAc) (Reich, *Helv. Chim. Acta*, 1945, **28**, 863) and a second product which was not identified. Reduction with lithium aluminium hydride, followed by acetylation, furnished 3α : 12α : 20β-triacetoxypregnan-17α-ol (VII; R′ = Ac) and a small quantity of an isomer. Finally, dehydration with thionyl chloride–pyridine gave 3α : 12α-diacetoxypregn-16-en-20-one (V) (Djerassi and Scholz, *loc. cit.*). The formulation (X; R′ = Ac) is thus proved beyond reasonable doubt.

Hydrolysis of the compound (X; R′ = Ac) with methanolic potassium carbonate furnished the triol (X; R = α-OH, R′ = H) in 84% yield, the structure of this compound following from its reconversion into the diacetate and formation of a di-*p*-nitrobenzoate. In addition, ethyl chloroformate gave 3α-ethoxycarbonyloxy-12α : 17α-dihydroxypregnan-20-one (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = H) (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1950, **72**, 5530) which passed into 12α-acetoxy-3α-ethoxycarbonyloxy-17α-hydroxypregnan-20-one (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = Ac) on acetylation. Chromic acid oxidation, however, gave a complex ketonic mixture from which testane-3 : 12 : 17-trione (VIII; R = R′ = :O) could not be isolated [cf. (X; R′ = Ac) ⟶ (VIII); also (d) (vii)].

With 1 mol. of bromine 3α : 12α : 17α-trihydroxypregnan-20-one (X; R = α-OH, R′ = H) furnished the unstable bromo-derivative (XI; R = α-OH, R′ = H, R″ = Br) and thence the 21-iodide and 21-acetate (XI; R = α-OH, R′ = H, R″ = Ac). Oxidation of the last compound with *N*-bromoacetamide in aqueous *tert.*-butanol (Reich and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 562) gave 21-acetoxy-12α : 17α-dihydroxypregnane-3 : 20-dione [XI; R = :O, R′ = H, R″ = OAc; see (d) vii) for evidence regarding preferential oxidation of the 3-hydroxyl group in 3α : 12α : 17α-trihydroxypregnan-20-ones], which was characterised by acetylation to the 12α : 21-diacetate (XI; R = :O, R′ = Ac, R″ = OAc), also formed as described under (*b*) below. Careful bromination of the monoacetoxy-ketone gave exclusively the 4β-bromo-derivative (XII; R = H, R′ = OAc; cf. Fieser and Ettore, *J. Amer. Chem. Soc.*, 1953, **75**, 1700, p. 1700). The last stage of the partial synthesis was accomplished by dehydrobromination of the last by Kendall's method (Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287) as modified by Kritchevsky, Garmaise, and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 483) to give the required 21-acetoxy-12α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XVI; R = H, R′ = OAc) in satisfactory yield.

(b) *Preparation of* 12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = Ac, R′ = OAc).—Partial hydrolysis of 3α : 12α-diacetoxypregn-16-en-20-one (V) furnished the 12α-acetoxy-3α-hydroxy-compound, reconverted into (V) by acetylation and characterised as the 3-*p*-nitrobenzoate. Epoxidation gave 12α-acetoxy-16α : 17α-epoxy-3α-hydroxypregnan-20-one (VI; R = α-OH, R′ = Ac, R″ = H) which formed a 3-*p*-nitrobenzoate. Treatment of this oxide with hydrobromic acid–acetic acid at −18° for 20 hours led to the formation of 12α-acetoxy-16β-bromo-3α : 17α-dihydroxypregnan-20-one in moderate yield. Reductive removal of the the 16β-bromine atom gave 12α-acetoxy-3α : 17α-dihydroxypregnan-20-one (X; R = α-OH, R′ = Ac) and thence 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one (X; R′ = Ac) identical with material described under (*a*). With one equivalent of bromine, (X; R = α-OH, R′ = Ac) furnished the unstable 21-bromide (XI; R = α-OH, R′ = Ac, R″ = Br) which decomposed on attempted purification [cf. (*d*) (vi) for observations regarding the lability of the 12α-acetyl group in 12α-acetoxy-17α-hydroxypregnan-20-ones)]. It was therefore converted *via* the iodide into 12α : 21-diacetoxy-3α : 17α-dihydroxypregnan-20-one (XI; R = α-OH, R′ = Ac, R″ = OAc) and the constitution of this was confirmed by acetylation to (XI; R′ = Ac, R″ = OAc), also formed as described in (*c*) below. Oxidation of the diacetate (XI; R = α-OH, R′ = Ac, R″ = OAc with *N*-bromoacetamide in aqueous *tert.*-butanol gave the 3 : 20-dione (XI; R = :O, R′ = Ac, R″ = OAc) described in (*a*) above. Bromination at $C_{(4)}$, followed by dehydrobromination, led to 12α : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione (XVI; R = Ac, R′ = OAc), identical with material prepared by route (*a*).

(c) *Preparation of* 3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—Alternative routes to this compound were developed in order to compare the product thus obtained with material prepared as in (*b*).

(i) Monobromination of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one (X; R′ = Ac) gave a sticky bromo-compound which was converted into the 21-iodide and thence in low yield into 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one (XI; R′ = Ac, R″ = OAc).

(ii) 3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (VI; R′ = Ac, R″ = H) (see above) and hydrogen bromide in acetic acid at room temperature gave the 16β-bromide (IX; R′ = H) [cf. (*a*)], which was treated *in situ* with one mol. of bromine, yielding the 16β : 21-dibromo-compound (IX; R′ = Br). Replacement of the 21-bromine atom by acetoxyl in the last compound was effected by means of potassium acetate in hot acetone and was accompanied by regeneration of the epoxide ring with formation of 3α : 12α : 21-triacetoxy-16α : 17α-epoxypregnan-20-one (VI; R′ = Ac, R″ = OAc) (cf. Julian *et al.*, *loc. cit.*). Reaction with hydrogen bromide cleaved the epoxide ring with formation of the bromohydrin (IX; R′ = OAc), which passed into 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one (XI; R′ = Ac, R″ = OAc) when heated with Raney nickel in ethanol.

(d) *Miscellaneous.*—(i) Attempts to employ Wagner and Moore's method for building up the cortical side chain (*ibid.*, 1949, **71**, 4160) were not successful. Reaction of (I) with 3 mols. of bromine gave the tribromide (II) [see (*a*)], which passed into 20-bromo-3α : 12α-dihydroxypregn-17-en-21-oic acid (III; R = R′ = α-OH, R″ = H) on Favorski rearrangement. Esterification with diazomethane gave the methyl ester which was characterised by conversion into the diacetate (III; R′ = α-OAc, R″ = Me), and by oxidation to methyl 20-bromo-12α-hydroxy-3-oxopregn-17-en-21-oate (III; R = :O, R′ = α-OH, R″ = Me) with aluminium *tert.*-butoxide in *cyclo*hexanone–toluene and to methyl 20-bromo-3 : 12-dioxopregn-17-en-21-oate (III; R = R′ = :O, R″ = Me) with chromic–acetic acid. Reduction with lithium aluminium hydride gave 20-bromo-3α : 12α : 21-trihydroxypregn-17-ene. The triacetate (IV) of this compound, however, was recovered unchanged after treatment with osmium tetroxide or with hydrogen peroxide–osmium tetroxide (Miescher and Schmidlin, *Helv. Chim. Acta*, 1950, **33**, 1840).

(ii) Sarett's cyanohydrin procedure (*J. Amer. Chem. Soc.*, 1948, **70**, 1454) for introducing the 17α-hydroxyl group into pregnan-20-ones gave discouraging results. Conversion of diacetoxypregnan-20-one (I) into the cyanohydrin by reaction with potassium cyanide in ethanolic acetic acid did not proceed as readily as in the pregnane-11 : 20-dione series, the desired compound being obtained in only 25% yield (allowing for recovery of unchanged material). Its dehydration with phosphorus oxychloride was also difficult, 3α : 12α-diacetoxy-20-cyanopregn-17-ene (XIII; R′ = CN) being obtained in too low a yield to warrant a further study. Even less satisfactory results attended the use of 3α : 12α : 21-triacetoxypregnan-20-one (XIV) (Meystre and Wettstein, *Helv. Chim. Acta*, 1947, **30**, 1037) as starting material : the yield of cyanohydrin could not be raised above *ca.* 12% (allowing for recovered starting material), and dehydration failed to give a product with a satisfactory analysis.

(iii) Gallagher's enol acetate method (*J. Amer. Chem. Soc.*, 1949, **71**, 3262) for preparing 17α-hydroxy-pregnan-20-ones could not be applied to 12α-acetoxypregnan-20-ones : 3α : 12α : 20-triacetoxypregn-17-ene (XIII; R′ = OAc) failed to react with perbenzoic acid, perphthalic acid, or hydrogen peroxide–osmium tetroxide (Miescher and Schmidlin, *loc. cit.*). Performic acid, in contrast, proved too vigorous, degrading the compound to 3α : 12α-diacetoxytestan-17-one (VIII; R′ = α-OAc), which was hydrolysed to 3α : 12α-dihydroxytestan-17-one (VIII; R = R′ = α-OH) and then converted into testane-3 : 12 : 17-trione (VIII; R = R′ = :O).

Hirschmann, Brown, and Wendler (*ibid.*, 1951, **73**, 5373) had previously shown that the 12-oxo-group fails to undergo enol-acetylation. So we studied 3-ethoxycarbonyloxy- and 3α-acetoxy-pregnane-12 : 20-dione in which the 12α-acetoxy-residue is replaced by the smaller keto-group. In this way we hoped to avoid the steric hindrance effects presumably exercised by the 12α-acetoxyl group on the epoxidation of (XIII; R′ = OAc).

3α : 12α-Dihydroxypregnan-20-one gave an excellent yield (cf. Fieser, Herz, Klohs, Romero, and Utne, *ibid.*, 1952, **74**, 3309) of the 3α-ethoxycarbonyloxy-derivative, smoothly

oxidised by *N*-bromosuccinimide in *tert.*-butanol to the 12 : 20-dione. Enol-acetylation with acetic anhydride–toluene-*p*-sulphonic acid, followed by reaction of the total product with perbenzoic acid and subsequent hydrolysis, failed to yield the desired 17α-hydroxy-derivative, although reaction with the peracid undoubtedly occurred. Similar results were obtained with 3α-acetoxypregnane-12 : 20-dione, which was conveniently prepared by partial oxidation of 3α : 12α-dihydroxypregnan-20-one with potassium chromate–acetic acid to the 12-keto-derivative, followed by acetylation.

(iv) Conversion of (I) into the $C_{(20)}$-enol ether (XIII; R′ = OEt) was examined as it was hoped that this compound would undergo epoxidation with formation of (X; R′ = Ac). By reaction with ethyl orthoformate in the presence of sulphuric or toluene-*p*-sulphonic acid 3α : 12α-diacetoxy-20-ethoxypregn-17(or 20)-ene (XIII; R′ = OEt) was obtained in *ca.* 12% yield. Treatment with perbenzoic acid failed to give the 17α-hydroxy-derivative, vigorous reaction accompanied by side-chain degradation taking place. Belleau and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 2816) have since described the conversion of (11-oxo) pregnanolone into a mixture of the Δ^{17}- and Δ^{20}-enol ethers, which were severally degraded to the (11-oxo) 17-keto-steroid and ethyl ester of etianic acid by perbenzoic acid.

(v) Julian *et al.* (*loc. cit.*) converted 21-acetoxy-16β-bromo-17α-hydroxypregn-4-ene-3 : 20-dione into compound S acetate by Raney nickel in hot ethanol. By this reaction, (IX; R′ = H) gave yields varying from 3% to 70%. We consequently studied the conversion of (IX; R′ = H) into (X; R′ = Ac) in some detail.

Chemical methods of reduction failed to effect the required change. Zinc dust or activated zinc in boiling ethanol led to (V). No reaction occurred with zinc dust, chromous chloride, or Raney nickel at room temperature, or with sodium iodide in boiling acetone. Silver nitrate–pyridine had no effect at room temperature, but produced the epoxide (VI; R′ = Ac, R″ = H) after brief heating at 100°. Attempts to cleave the epoxide ring with thiourea–toluene-*p*-sulphonic acid (King and Campbell, *ibid.*, 1949, **71**, 3556) gave a sulphur-free product which failed to crystallise. Thiolacetic acid and pyridine hydrobromide (cf. Mancera, Rosenkranz, and Djerassi, footnote p. 1280 to Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278) were without effect, as was hydrogen iodide under the conditions employed by Barton, Miller, and Young (*J.*, 1951, 2598). The method finally adopted for preparing 17α-hydroxypregnan-20-ones (X) from the epoxides (VI; R″ = H) lay in conversion into the bromohydrins (IX; R′ = H) followed by reductive removal of the 16β-bromine atom by catalytic hydrogenation over 2% palladium–calcium carbonate [cf. (*a*) above].

(vi) Partial hydrolysis of (X; R′ = Ac) would give 12α-acetoxy-3α : 17α-dihydroxy-pregnan-20-one (X; R = α-OH, R′ = Ac). With the 12α-OH group thus protected, the way would have been open to the introduction of the 21-acetoxyl group, etc. 0·3N-Sodium hydroxide (1 hour) or methanolic potassium carbonate (1 equiv. for 12 hours) at room temperature and methanolic hydrochloric acid (1 hour) under reflux, which convert (I) into the 12α-acetoxy-3α-hydroxy-derivative, gave the fully hydrolysed product (X; R = α-OH, R′ = H). This atypical behaviour probably arises from the close proximity of the 17α-hydroxy-group to the 12α-acetoxy-group with consequent hydrogen bonding and lability (cf. Petrow, Rosenheim, and Starling, *J.*, 1943, 135).

(vii) We had previously found that *N*-bromoacetamide in aqueous *tert.*-butanol (Reich and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 562) effects smooth conversion of 3α : 12α-dihydroxypregnan-20-one into pregnane-3 : 12 : 20-trione. We applied this reaction to 3α : 12α : 17α-trihydroxypregnan-20-one (X; R = α-OH; R′ = H) as attempts to confirm its structure by chromic acid oxidation to testane-3 : 12 : 17-trione had failed [see (*a*)]. The product, however, was clearly not the expected 17α-hydroxypregnane-3 : 12 : 20-trione, as it gave a monoacetate smoothly and quantitatively; as it did not give an ethoxycarbonyloxy-derivative it was formulated as 12α : 17α-dihydroxypregnane-3 : 20-dione (X; R = :O, R′ = H). In support of this structure we found that monobromination gave an excellent yield of 4β-bromo-12α : 17α-dihydroxypregnane-3 : 20-dione (XII; R = R′ = H), which passed into the αβ-unsaturated ketone 12α : 17α-dihydroxypregn-4-ene-3 : 20-dione (XVI; R = R′ = H), characterised as the monoacetate.

(viii) Reduction of (XIV) with lithium aluminium hydride followed by acetylation of the

total product and chromatography gave 3α : 12α : 20ξ : 21-tetra-acetoxypregnane (XV; R′ = Ac), readily hydrolysed to a pregnane-3α : 12α : 20ξ : 21-tetraol (XV; R = α-OH, R′ = H). Molecular-rotational data appeared to indicate an α-configuration at $C_{(20)}$. This conclusion, however, makes no allowance for the strong vicinal effect, clearly revealed by infra-red studies, which the 12α-acetoxyl group exerts on the polar residues in the side chain.

(ix) Reduction of the epoxide (VI; R′ = Ac, R″ = OAc) with lithium aluminium hydride furnished pregnane-3α : 12α : 17α : 20ξ : 21-pentaol in unsatisfactory yield. The compound was characterised as a tetra-acetate, but its conversion into (XI; R′ = Ac, R″ = OAc) [cf. (*c*)] was not proceeded with in view of results described above.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube unless otherwise stated. Ultra-violet absorption spectra (in *iso*propanol) were kindly determined by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc. Alumina, B.D.H., chromatography grade, was used.

3α : 12α-*Diacetoxy*-17 : 21 : 21-*tribromopregn*-20-*one* (II).—Diacetoxypregnanone (I) (12·5 g.) in glacial acetic acid (400 ml.) containing hydrogen bromide in acetic acid (2 ml. of 50% w/v) was treated at 40° with stirring with a molar solution of bromine in acetic acid (60 ml.) at such a rate that the bromine colour did not persist. The temperature was then raised to 70° and a further quantity of bromine solution (30 ml.) added, stirring with temperature control being maintained for a further 30 min. The mixture was then poured into water and the precipitated solids were collected, washed, dried, and purified from aqueous acetone. 3α : 12α-*Diacetoxy*-17 : 21 : 21-*tribromopregnan*-20-*one* had m. p. 174—175° (decomp.), $[\alpha]_D^{23}$ +74° (*c*, 0·102) (Found : C, 45·9; H, 5·2; Br, 36·0. $C_{25}H_{35}O_5Br_3$ requires C, 45·8; H, 5·3; Br, 36·6%).

3α : 12α-*Diacetoxypregn*-16-*en*-20-*one* (V).—The foregoing compound (15 g.) in acetic acid (200 ml.) was warmed on a steam-bath with sodium iodide (30 g.) for 30 min. The product precipitated in water was extracted with ether, which was washed successively with water, 20% potassium metabisulphite solution, 20% sodium thiosulphate solution, water, sodium hydrogen carbonate solution, and water. After being dried, the ethereal solution was evaporated to small bulk and *n*-hexane was added; 3α : 12α-*diacetoxypregn*-16-*en*-20-*one* crystallised, having m. p. 190—192° (Found : C, 72·0; H, 8·9. Calc. for $C_{25}H_{36}O_5$: C, 72·1; H, 8·7%). The crude bromo-compound was used for preparation of (V) in quantity.

3α : 12α-*Diacetoxy*-16α : 17α-*epoxypregnan*-20-*one* (VI; R′ = Ac, R″ = H).—3α : 12α-Diacetoxypregn-16-en-20-one (10 g.) in methanol (400 ml.) was treated at 0° with 4N-sodium hydroxide (20 ml.) and hydrogen peroxide (40 ml. of 30%). After 24 hr. at room temperature the solution was diluted with a large volume of water, neutralised with acetic acid, and extracted with ether. The extract was washed with sodium iodide solution, sodium thiosulphate solution, and water, dried, and evaporated. The residue was purified from *n*-hexane. 3α : 12α-*Diacetoxy*-16α : 17α-*epoxypregnan*-20-*one* formed prisms, m. p. 119—121°, $(\alpha)_D^{30}$ +92° (*c*, 2·324 in EtOH) (Found : C, 69·1; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

Pregnane-3α : 12α : 17α : 20β-*tetraol* (VII; R = α-OH).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (850 mg.) in dry ether (40 ml.) was added dropwise with stirring during 15 min. to lithium aluminium hydride (600 mg.) in ether (60 ml.). After 30 minutes' heating under reflux the mixture was decomposed with ice-water and acidified with 10% aqueous sulphuric acid, and the product extracted with ether–chloroform. Purification from aqueous methanol gave *pregnane*-3α : 12α : 17α : 20β-*tetraol*, needles, m. p. 262—264°, $[\alpha]_D^{23}$ +30° (*c*, 0·672 in EtOH) (Found : C, 71·5; H, 10·3. $C_{21}H_{36}O_4$ requires C, 71·6; H, 10·2%).

The triacetate formed needles, m. p. 191—192°, $[\alpha]_D^{23}$ +133° (*c*, 0·302), from aqueous methanol. It was also obtained by treating (VI; R′ = Ac, R″ = H) (500 mg.) in ethanol (5 ml.) and 0·2N-sodium hydroxide (6 ml.) at 0° with sodium borohydride (100 mg.). After 18 hr. at 5°, the mixture was diluted with water, and the product extracted with chloroform, giving an oil (500 mg.). This was acetylated and purified by chromatography on alumina (15 g.) from which the triacetate was obtained by elution with benzene and benzene–ether.

3α : 12α-*Diacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = H).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (10 g.) in glacial acetic acid (55 ml.) was treated with hydrogen bromide in acetic acid (6 ml. of 50%) for 30 min. at room temperature; the mixture was then diluted with water, and the precipitated solids were collected, washed, and dried *in vacuo* over potassium hydroxide. Crystallisation from acetone–hexane gave 3α : 12α-*diacetoxy*-16β-

bromo-17α-*hydroxypregnan*-20-*one*, needles, m. p. 166—168°, $[\alpha]_D^{23}$ +193° (*c*, 1·506) (Found: C, 58·9; H, 7·4; Br, 15·3. $C_{25}H_{37}O_6Br$ requires C, 58·5; H, 7·3; Br, 15·6%).

3α : 12α-*Diacetoxy*-17α-*hydroxypregnan*-20-*one* (X; R′ = Ac).—(i) The foregoing compound (5 g.) in 95% ethanol (200 ml.) was stirred with Raney nickel (25 g., prepared as described in Adkins's " Reactions of Hydrogen," University of Wisconsin Press, Wisconsin, 1937) on a steam-bath for 5 hr. The hot solution was filtered (Hyflo), the residue thoroughly washed with ethanol, and the filtrate taken to dryness under reduced pressure. The residue was chromatographed in benzene on alumina (100 g.). Elution with benzene and benzene–ether furnished 3α : 12α-*diacetoxy*-17α-*hydroxypregnan*-20-*one*, needles, m. p. 74—77° or 104—105°, $[\alpha]_D^{22}$ +128° (*c*, 0·496) (Found: C, 69·4; H, 9·0. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

(ii) The bromohydrin (5 g.) in 90% methanol (250 ml.) was catalytically hydrogenated over 2% palladium–calcium carbonate (10 g.). After removal of the catalyst, the solution was partially evaporated, and the residue extracted with ether. Crystallisation from hexane gave (X; R′ = Ac).

Acetylation of the foregoing compound (1 g.) in pyridine (15 ml.) and acetic anhydride (10 ml.) under reflux for 2 hr., followed by chromatography in benzene (10 ml.) on alumina (30 g.) and elution with ether–benzene (10 ⟶ 40%) gave unchanged starting material. From 50% ether–benzene to acetone eluates a small quantity of crystals, m. p. 203°, was obtained. A further amount was isolated by rechromatography of the mother-liquors from the first fractions. The compound, crystallised from acetone–hexane, had m. p. 203° (Found: C, 67·7; H, 8·5. 3α : 12α : 17α-*Triacetoxypregnan*-20-*one*, $C_{27}H_{40}O_7$, requires C, 68·1; N, 8·4%).

Oxidation of 3α : 12α-*Diacetoxy*-17α-*hydroxypregn*-20-*one*.—The compound (500 mg.) in glacial acetic acid (7·75 ml.) was treated with chromic acid (10·1 ml. of 2% solution in 90% acetic acid) for 5 hr. at room temperature. The neutral fraction of the oxidation product (520 mg.) failed to crystallise. It was chromatographed in benzene on alumina (15 g.). From 30% to 50% ether–benzene eluates 3α : 12α-diacetoxytestan-17-one (*ca.* 100 mg.) was obtained, having m. p. 156—157°, $[\alpha]_D^{19}$ +181° (*c*, 0·432 in acetone) (Found: C, 71·1; H, 8·8. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%), not depressed on admixture with an authentic specimen (Reich, *loc. cit.*). By rechromatography of the first fractions a further quantity was obtained from 30% to 50% ether–benzene eluates. Benzene to ether–benzene (10% to 30%) eluates gave a product (*ca.* 100 mg.), needles or plates, m. p. 158—159°, $[\alpha]_D^{19}$ +90° (*c*, 0·376 in acetone) (Found: C, 69·1; H, 8·4%).

Hydrolysis of 3α : 12α-diacetoxytestan-17-one with methanolic sodium hydroxide furnished 3α : 12α-dihydroxytestan-17-one, m. p. 144° and 163—164° (Found: C, 74·5; H, 9·8. Calc. for $C_{19}H_{30}O_3$: C, 74·5; H, 9·8%).

Testane-3 : 12 : 17-*trione* (VIII; R = R′ = :O).—3α : 12α-Dihydroxytestan-17-one (100 mg.) in acetic acid (3·6 ml.) was stirred at room temperature for 25 hr., chromic acid (3·6 ml. of 2% solution in acetic acid) being added at the start of the reaction and after 4, 8, and 23 hr. The mixture was then poured into water, and the product isolated with ether and crystallised from benzene–light petroleum. Testane-3 : 12 : 17-trione formed crystals, m. p. 268—270°, not depressed on admixture with an authentic specimen (Reich, *loc. cit.*).

Reduction of 3α : 12α-*Diacetoxy*-17α-*hydroxypregnan*-20-*one*.—3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (200 mg). in ether (20 ml.) was added to a boiling suspension of lithium aluminium hydride (150 mg.) in ether (25 ml.). After a further 30 min., the mixture was decomposed with ice-water, acidified to Congo-red with dilute sulphuric acid, and extracted with chloroform (3 × 80 ml.). The solids obtained therefrom were acetylated with acetic anhydride (2·5 ml.)–pyridine (2·5 ml.) and chromatographed in benzene on alumina (3 g.). Early ether–benzene eluates gave 3α : 12α : 20β-triacetoxypregnan-17α-ol, m. p. 191—192°, alone or on admixture with a sample prepared as above. From later acetone–ether and acetone eluates a substance was obtained, m. p. 268—273°, identical with that prepared by the reduction of 3α : 12α-diacetoxy-16β-bromo-17α-hydroxypregnan-20-one with a very active Raney nickel catalyst and tentatively formulated as 3α : 12α-diacetoxy-17α : 20α-dihydroxypregnane.

Dehydration of 3α : 12α-*Diacetoxy*-17α-*hydroxypregnan*-20-*one*.—The compound (100 mg.) in dry pyridine (1 ml.) was treated with thionyl chloride (0·03—0·05 ml.) at room temperature for 5 min., after which it was poured into water. Crystallisation of the precipitated solids from acetone–hexane furnished 3α : 12α-diacetoxypregn-16-en-20-one, needles, m.p. and mixed m. p. 190—191°, $\lambda_{max.}$ 237 mμ (log ε 4·0).

3α : 12α : 17a-*Trihydroxypregnan*-20-*one* (X; R = α-OH, R′ = H).—(i) 3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (8·13 g.) in methanol (320 ml.) was treated with potassium carbonate (1·5 g., 1·15 equiv.) in water (15 ml.) for 12 hr. at room temperature. After precipitation

with water the product was collected and purified from aqueous methanol. **3α : 12α : 17α-*Trihydroxypregnan*-20-*one*** formed needles, m. p. 193—194°, $[\alpha]_D^{24}$ +81° (*c*, 0·422) (Found : C, 71·9; H, 10·0. $C_{21}H_{34}O_4$ requires C, 72·0; H, 9·7%).

(ii) The same product was obtained by treating the diacetate (2 g.) in ethanol (500 ml.) with 0·6N-aqueous sodium hydroxide (500 ml.) for 1 hr. at room temperature.

(iii) **3α : 12α : 17α**-Trihydroxypregnan-20-one was also obtained by heating the diacetate (200 mg.) in methanol (5 ml.) with concentrated hydrochloric acid (0·15 ml.) for 1 hr. under reflux.

The *di*-p-*nitrobenzoate* formed needles, m. p. 208—210° (Found : C, 65·0; H, 7·1; N, 4·4. $C_{35}H_{40}O_{10}N_2$ requires C, 64·8; H, 6·2; N, 4·3%).

3α-*Ethoxycarbonyloxy*-12α : 17α-*dihydroxypregnan*-20-*one* (X; R = α-$EtO_2C{\cdot}O{\cdot}$, R′ = H), prepared by treatment of **3α : 12α : 17α**-trihydroxypregnan-20-one (500 mg.) in pyridine (3 ml.) with ethyl chloroformate (0·5 g.) with cooling, followed by reaction at room temperature overnight, formed needles, m. p. 216—217°, $[\alpha]_D^{23}$ +82° (*c*, 0·0586) (Found : C, 68·0; H, 8·9. $C_{24}H_{38}O_6$ requires C, 68·2; H, 9·0%), after crystallisation from aqueous methanol. Its *acetate*, after purification from acetone–hexane, formed crystals, m. p. 119—120°, $[\alpha]_D^{22}$ +119° (*c*, 0·428) (Found : C, 67·1; H, 8·6. $C_{26}H_{40}O_7$ requires C, 67·2; H, 8·6%).

21-*Bromo*-3α : 12α : 17α-*trihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = H, R″ = Br).—**3α : 12α : 17α**-Trihydroxypregnan-20-one (2 g.) in chloroform (60 ml.) at 40° was treated with stirring with a solution of bromine in chloroform (32 ml. of 0·138M) added dropwise during 20 min. Stirring was continued without external heating for a further 15 min. The solution was diluted with chloroform to 250 ml., washed with water, sodium hydroxide solution (5%), and water, dried, and evaporated. The residue was crystallised once from chloroform with as little heating as possible and the bromo-compound, needles, m. p. 113—115°, 169—172°, was used directly for the next stage of the partial synthesis.

21-*Acetoxy*-3α : 12α : 17α-*trihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = H, R″ = OAc).—The foregoing compound (1·51 g.) in dry acetone (100 ml.) was heated with sodium iodide (900 mg.) for 15 min. After filtration from sodium bromide the solution was heated with potassium hydrogen carbonate (7·6 g.) and acetic acid (4·36 ml.) under reflux for 12 hr. The mixture was then diluted with water, and the product isolated with ether. Crystallisation from acetone–hexane gave **21-*acetoxy*-3α : 12α : 17α-*trihydroxypregnan*-20-*one***, needles, m. p. 218—220°, $[\alpha]_D^{24}$ +72° (*c*, 0·402) (Found : C, 67·8; H, 8·8. $C_{23}H_{36}O_6$ requires C, 67·7; H, 8·8%).

21-*Acetoxy*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XI; R = :O, R′ = H, R″ = OAc).—The foregoing compound (500 mg.) and *N*-bromoacetamide (550 mg.) in *tert.*-butanol (10 ml.), pyridine (0·2 ml.), and water (0·2 ml.) were left at room temperature for 7 hr. After precipitation with water, the product was collected and purified from acetone–hexane. **21-*Acetoxy*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione*** formed needles, m. p. 221°, $[\alpha]_D^{24}$ +80° (*c*, 0·424) (Found : C, 67·9; H, 8·5. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

12α : 21-*Diacetoxy*-17α-*hydroxypregnane*-3 : 20-*dione* (XI; R = :O, R′ = Ac, R″ = OAc), prepared by acetylation of the foregoing compound, formed plates, m. p. 198°, $[\alpha]_D^{26}$ +122° (*c*, 0·430) (Found : C, 66·7; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·0%), from acetone–hexane.

21-*Acetoxy*-4-*bromo*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XII; R = H, R′ = OAc).—(i) 21-Acetoxy-**12α : 17α**-dihydroxypregnane-3 : 20-dione (270 mg.) in acetic acid (10 ml.) was treated with hydrogen bromide (1 drop of 50% solution in acetic acid) and bromine (0·68 ml.; 0·984M-solution in acetic acid). Rapid absorption of bromine occurred. After 15 min. the mixture was precipitated with water, and the bromo-compound isolated with ether. The bromo-compound formed needles, m. p. 188—189° (decomp.), on crystallisation from acetone–hexane with as little heating as possible. It was used immediately.

(ii) 21-Acetoxy-**12α : 17α**-dihydroxypregnane-3 : 20-dione (3 g.) in acetic acid (75 ml.) was treated with stirring at room temperature with bromine in acetic acid (0·6 ml.; 0·98M) and hydrogen bromide in acetic acid (1 drop of 50% solution). When decolorisation was complete a mixture of bromine in acetic acid (6·99 ml.; 0·98M) and anhydrous sodium acetate in acetic acid (7·38 ml.; 0·92N) was added at such a rate that the solution remained colourless (*ca.* 5 min.). After dilution with water the mixture was extracted with ether, which was washed with water, aqueous sodium carbonate, and water, and dried. Evaporation gave the bromo-derivative which was too unstable for analysis.

21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = H, R′ = OAc).—The foregoing bromo-derivative (160 mg.) in acetic acid (30 ml. of 98%) was heated with semicarbazide hydrochloride (110 mg.) and anhydrous sodium acetate (110 mg.) at 70° for 2 hr. in an atmosphere of nitrogen. Pyruvic acid (1·62 ml.) in water (3·25 ml.) was then added and the temperature kept at 70° for a further 2 hr. After dilution with water the product was isolated

with ether and purified from acetone–hexane. 21-*Acetoxy*-12α : 17α-*dihydroxypregn*-4-*ene*-3 : 20-*dione* formed needles, m. p. 195—197°, $[\alpha]_D^{24}$ +146° (*c*, 0·422), $\lambda_{max.}$ 240 mμ (log ε 4·21) (Found : C, 68·3; H, 8·0. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·9%).

Acetylation gave 12α : 21-*diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione*, plates, m. p. 179°, $[\alpha]_D^{26}$ +192° (*c*, 0·428) (Found : C, 66·7; H, 7·5. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·6%), after crystallisation from acetone–hexane.

12α-*Acetoxy*-3α-*hydroxypregn*-16-*en*-20-*one* (V; R = α-OH), prepared by heating 3α : 12α-diacetoxypregn-16-en-20-one (1·5 g.) in methanol (50 ml.) with potassium carbonate (300 mg.) in water (5 ml.) for 1 hr. under reflux under nitrogen, formed needles, m. p. 195—197°, $[\alpha]_D^{25}$ +117° (*c*, 0·94) (Found : C, 73·8; H, 9·1. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·2%), from acetone–hexane. The 3-p-*nitrobenzoate* (from methanol) had m. p. 237—239° (Found : C, 68·4; H, 7·1; N, 2·1. $C_{30}H_{37}O_7N$ requires C, 68·8; H, 7·1; N, 2·7%).

12α-*Acetoxy*-16α : 17α-*epoxy*-3α-*hydroxypregnan*-20-*one* (VI; R = α-OH, R″ = H; R′ = Ac), prepared by treating 12α-acetoxy-3α-hydroxypregn-16-en-20-one (7 g.) in methanol (900 ml.) and water (105 ml.) at 0° with cooled 30% hydrogen peroxide (87 ml.) and 5% sodium carbonate solution (14 ml.) for 16 hr. at 0°, had m. p. 97—103° (Found : C, 71·5; H, 8·5. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), after crystallisation from benzene–hexane. The 3-p-*nitrobenzoate* separated from benzene–hexane in needles, m. p. 223—225° (Found : C, 66·1; H, 6·6; N, 2·0. $C_{30}H_{37}O_8N$ requires C, 66·8; H, 6·9; N, 2·6%).

12α-*Acetoxy*-16β-*bromo*-3α : 17α-*dihydroxypregnan*-20-*one*, prepared by treatment of 12α-acetoxy-16α : 17α-epoxy-3α-hydroxypregnan-20-one (1 g.) in chloroform (22 ml.) with hydrobromic acid in acetic acid (2·5 ml. of saturated solution + 7·5 ml. of acetic acid) at −18° for 20 hr., had m. p. 165—166° or 172—173°, $[\alpha]_D^{22}$ +109° (*c*, 0·39) (Found : C, 58·1; H, 7·5; Br, 17·8. $C_{23}H_{35}O_5Br$ requires C, 58·6; H, 7·4; Br, 17·0%) after crystallisation from acetone–hexane.

12α-*Acetoxy*-3α : 17α-*dihydroxypregnan*-20-*one* (X; R = α-OH, R′ = Ac) was prepared from the foregoing compound by catalytic hydrogenation in aqueous methanol (10% of H_2O) with 2% palladium–calcium carbonate. Crystallisation from acetone–hexane gave needles, m. p. 167—169°, $[\alpha]_D^{23}$ +116° (*c*, 0·438) (Found : C, 67·6; H, 9·4. $C_{23}H_{36}O_5,H_2O$ requires C, 67·3; H, 9·0%). The 3-p-*nitrobenzoate* formed needles, m. p. 216—218° (Found : C, 66·6; H, 7·3; N, 2·2. $C_{30}H_{39}O_8N$ requires C, 66·6; H, 7·2; N, 2·5%).

12α-*Acetoxy*-21-*bromo*-3α : 17α-*dihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = Ac, R″ = Br).—A solution of bromine in acetic acid (15·75 ml.; 0·195M) was added to one of 12α-acetoxy-3α : 17α-dihydroxypregnan-20-one (1·236 g.) containing 2 drops of hydrogen bromide in acetic acid, stirred at 30°, at such a rate that each drop was immediately decolorised. Stirring was continued for a further 30 min., after which the mixture was poured into water and the bromo-compound isolated with ether and used without further purification.

12α : 21-*Diacetoxy*-3α : 17α-*dihydroxypregnan*-20-*one* (XI; R = α-OH, R′ = Ac, R″ = OAc).—The foregoing crude bromo-compound was heated under reflux for 15 min. with sodium iodide (1·5 g.) in acetone (42 ml.). The cooled solution was filtered, the residue was washed with acetone (10 ml.), and the combined acetone filtrates were heated with potassium hydrogen carbonate (6·2 g.) and acetic acid (4 ml.) under reflux overnight. 12α : 21-*Diacetoxy*-3α : 17α-*dihydroxypregnan*-20-*one*, isolated with ether, formed needles, m. p. 236—238°, $[\alpha]_D^{22}$ +119° (*c*, 0·51) (Found : C, 66·8; H, 8·6. $C_{25}H_{38}O_7$ requires C, 66·7; H, 8·5%), on crystallisation from ethyl acetate and finally from chloroform–ether.

Oxidation with *N*-bromoacetamide gave (XI; R = :O, R′ = Ac, R″ = OAc).

12α : 21-*Diacetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = Ac, R′ = OAc).—12α : 21-Diacetoxy-17α-hydroxypregnane-3 : 20-dione was brominated with 1 mol. of bromine in acetic acid, to give 12α : 21-diacetoxy-4-bromo-17α-hydroxypregnane-3 : 20-dione, m. p. 112°, 151—153° (decomp.), after crystallisation from ether. The bromo-compound was not sufficiently stable for analysis and was used immediately. It was dehydrobrominated in the usual way, giving 12α : 21-diacetoxy-17α-hydroxypregn-4-ene-3 : 20-dione, m. p. 175° not depressed on admixture with a sample prepared as described above.

3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—3α : 12α-Diacetoxy-17α-hydroxypregnan-20-one (1 g.) in acetic acid (10 ml.) was treated with 50% hydrogen bromide in acetic acid (1 ml.), followed by 0·97M-bromine–acetic acid (2·6 ml.) at room temperature. Crystalline material separated. The mixture was kept at 40° for 30 min., then poured into water, and the bromo-compound isolated with ether. The resulting crude material was heated in dry acetone (75 ml.) with freshly fused potassium acetate (7·5 g.) for 5 hr. The product, isolated with ether, was chromatographed in benzene on alumina (25 g.). From 30% to 50% ether–benzene eluates, 3α : 12α : 21-*triacetoxy*-17α-*hydroxypregnan*-20-*one* was obtained,

having m. p. 140—141°, $[\alpha]_D^{22\cdot6}$ +138° (*c*, 0·458) (Found : C, 65·6; H, 7·9. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·1%).

3α : 12α-*Diacetoxy*-16β : 21-*dibromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = Br).—3α : 12α-Diacetoxy-16α : 17α-epoxypregnan-20-one (6·4 g.) in acetic acid (32 ml.) was left at room temperature for 20 min. with 50% w/v hydrobromic acid–acetic acid (4·3 ml.). 0·97M-Bromine–acetic acid (17 ml.) was then added during 15 min. at 40°. Temperature control was maintained for a further hour, then the mixture was poured into water. The precipitated solids, on purification from aqueous acetone, yielded 3α : 12α-*diacetoxy*-16β : 21-*dibromo*-17α-*hydroxypregnan*-20-*one*, needles, m. p. 192—194°, $[\alpha]_D^{20}$ +85° (*c*, 0·572) (Found : C, 50·1; H, 6·3; Br, 26·6. $C_{25}H_{36}O_6Br_2$ requires C, 50·7; H, 6·1; Br, 27·0%).

3α : 12α : 21-*Triacetoxy*-16α : 17α-*epoxypregnan*-20-*one* (VI; R′ = Ac, R″ = OAc).—The foregoing compound (4 g.) was heated with fused potassium acetate (22 g.) in dry acetone (200 ml.) under reflux for 4½ hr. The product, isolated with ether, was purified from acetone–hexane to give 3α : 12α : 21-*triacetoxy*-16α : 17α-*epoxypregnan*-20-*one*, m. p. 154—155°, $[\alpha]_D^{20}$ +85° (*c*, 0·564) (Found : C, 66·0; H, 7·9. $C_{27}H_{38}O_8$ requires C, 66·1; H, 7·8%).

3α : 12α : 21-*Triacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* (IX; R′ = OAc).—3α : 12α : 21-Triacetoxy-16α : 17α-epoxypregnan-20-one (550 mg.) in glacial acetic acid (3 ml.) was treated with 30% w/v hydrogen bromide–acetic acid (1 ml.) at room temperature for 30 min. The mixture was poured into water, and the precipitated solids were collected, washed, dried, and purified from aqueous methanol. 3α : 12α : 21-*Triacetoxy*-16β-*bromo*-17α-*hydroxypregnan*-20-*one* had m. p. 93° and 167—168°, $[\alpha]_D^{20}$ +119° (*c*, 0·456) (Found : C, 56·2; H, 6·6; Br, 13·5. $C_{27}H_{39}O_8Br$ requires C, 56·7; H, 6·8; Br, 14·0%).

3α : 12α : 21-*Triacetoxy*-17α-*hydroxypregnan*-20-*one* (XI; R′ = Ac, R″ = OAc).—The foregoing compound (460 mg.) in 95% ethanol (15 ml.) was heated with Raney nickel (2 g.) with stirring under reflux for 5 hr. The mixture was filtered hot through Hyflo, which was thoroughly washed with ethanol. The filtrate and washings were evaporated to dryness and the resulting oil was chromatographed in benzene on alumina (10 g.). Benzene–ether eluates furnished 3α : 12α : 21-triacetoxy-17α-hydroxypregnan-20-one, m. p. 141°, $[\alpha]_D^{22}$ +137° (*c*, 0·478) (Found : C, 65·3; H, 7·7. Calc. for $C_{27}H_{40}O_8$: C, 65·8; H, 8·1%), not depressed on admixutre with a specimen prepared as above.

20-*Bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oic acid* (III; R = R′ = α-OH, R″ = H).—Finely powdered 3α : 12α-diacetoxy-17 : 21 : 21-tribromopregnan-20-one (22·7 g.) in ethanol (360 ml.) was shaken with 10% potassium hydroxide solution (280 ml.) for 18 hr. at room temperature. The filtered solution was concentrated *in vacuo*, water added, and the solution acidified with dilute sulphuric acid to Congo-red. The precipitated solids were collected, washed with water, and dried, and a portion crystallised from methanol–ether. 20-*Bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oic acid* formed plates, m. p. 249—251° (Found: C, 59·0; H, 7·5; Br, 18·8. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·3; Br, 18·7%).

Methyl 20-*bromo*-3α : 12α-*dihydroxypregn*-17-*en*-21-*oate* (III; R = R′ = α-OH; R″ = Me), prepared from the crude acid (9·5 g.) in ether (150 ml.) and excess of diazomethane at room temperature (24 hr.), formed needles, m. p. 192—193°, $[\alpha]_D^{28}$ +84° (*c*, 0·998) (Found : C, 59·8; H, 7·5; Br, 18·4. $C_{22}H_{33}O_4Br$ requires C, 59·8; H, 7·5; Br, 18·1%), from aqueous methanol.

Methyl 20-*Bromo*-12α-*hydroxy*-3-*oxopregn*-17-*en*-21-*oate* (III; R = :O, R′ = α-OH, R″ = Me).—Methyl 20-bromo-3α : 12α-dihydroxypregn-17-en-21-oate (850 mg.) was dissoved in a solution of aluminium *tert.*-butoxide in benzene (9 ml. of 20%) and the benzene removed by distillation. Toluene (7 ml.) and *cyclo*hexanone (6 ml.) were added and the mixture was heated under reflux for 20 min. After acidification with dilute sulphuric acid, the organic solvents were removed in steam during 3 hr. The residue, isolated with ether, was purified from chloroform–hexane. Methyl 20-bromo-12α-hydroxy-3-oxopregn-17-en-21-oate formed crystals, m. p. 196—199°, $[\alpha]_D^{23}$ +94° (*c*, 1·35).

Methyl 20-*Bromo*-3 : 12-*dioxopregn*-17-*en*-21-*oate* (III; R = R′ = :O; R″ = Me).—The dihydroxy-compound (1·3 g.) in glacial acetic acid (25 ml.) was treated with cooling at 10—15° with chromic acid (800 mg.) in acetic acid (16 ml.) and water (2 ml.), and the whole kept at room temperature for 1 hr., then poured into sulphite solution and extracted with ether. The neutral fraction, purified from benzene–hexane, gave *methyl* 20-*bromo*-3 : 12-*dioxopregn*-17-*en*-21-*oate*, m. p. 212—214°, $[\alpha]_D^{22}$ +243° (*c*, 1·15) (Found : C, 60·6; H, 6·6; Br, 18·0. $C_{22}H_{29}O_4Br$ requires C, 60·4; H, 6·6; Br, 18·3%).

20-*Bromopregn*-17-*ene*-3α : 12α : 21-*triol*, prepared by treating (III; R = R′ = α-OH, R″ = Me) (1·147 g.) in ether with excess of lithium aluminium hydride at room temperature for 2 hr., had m. p. 149—151°, $[\alpha]_D^{21}$ +56° (*c*, 0·3) (Found : C, 58·7; H, 8·4. $C_{21}H_{33}O_3Br,H_2O$

requires C, 58·5; H, 8·1%). Its *triacetate* (IV) had m. p. 146—147°, $[\alpha]_D^{21}$ +120° (*c*, 0·48) (Found: C, 60·2; H, 7·3; Br, 14·1. $C_{27}H_{39}O_6Br$ requires C, 60·4; H, 7·2; Br, 14·7%). It failed to react with osmic acid in ethereal solution.

3α : 12α-*Diacetoxypregnan-20-one Cyanohydrin.*—3α : 12α-Diacetoxypregnan-20-one (1·88 g.) in ethanol (17 ml.) and acetic acid (6·4 ml.) was treated with potassium cyanide (6 g.) added portionwise with stirring at 0°. After a further ½ hr. at 0°, stirring was continued at room temperature for 2 hr., the mixture was poured into water, and the product extracted with ethyl acetate. Crystallisation from benzene–light petroleum gave the *cyanohydrin* (270 mg.), m. p. 190—191°, $[\alpha]_D^{23}$ +105° (*c*, 1·916) (Found: C, 69·4; H, 8·8; N, 3·2. $C_{26}H_{39}O_5N$ requires C, 7·01; H, 8·8; N, 3·2%). Chromatography of the residues led to recovery of 40% of (I).

3α : 12α-*Diacetoxy-20-cyanopregn-17-ene* (XIII; R′ = CN).—The foregoing cynaohydrin (200 mg.) in pyridine (3 ml.) was treated with phosphorus oxychloride (0·2 ml.). After being kept overnight the mixture was poured into water (60 ml.) and extracted with benzene (60 ml.). The benzene solution was washed successively with water, dilute acid, and water, and dried, and the solvent was removed. The residual oil (185 mg.) in benzene (2 ml.) was chromatographed on alumina (4 g.). The first benzene eluates gave 3α : 12α-*diacetoxy-20-cyanopregn-17-ene*, m. p. 188—191°, $[\alpha]_D^{23}$ +184° (*c*, 0·09) (Found: C, 73·2; H, 8·6; N, 3·3. $C_{26}H_{37}O_4N$ requires C, 73·1; H, 8·6; N, 3·3%), after crystallisation from aqueous methanol.

3α : 12α : 21-*Triacetoxypregnan-20-one cyanohydrin*, prepared as above from the appropriate ketone, had m. p. 176—178°, $[\alpha]_D^{20}$ +99° (*c*, 0·3772) (Found: C, 67·1; H, 8·1; N, 3·1. $C_{28}H_{41}O_7N$ requires C, 66·8; H, 8·2; N, 2·8%), after purification from benzene–light petroleum. Dehydration gave a *product*, m. p. 152—153° (Found: C, 68·3; H, 8·5; N, 1·2. $C_{28}H_{39}O_6N$ requires C, 69·3; H, 8·0; N, 2·9%).

3α : 12α-*Diacetoxytestan-17-one* (VIII; R′ = α-OAc).—3α : 12α : 20-Triacetoxypregn-17-ene (2·19 g.) was treated with perhydrol (2·2 ml.) and formic acid (21·9 ml.) for 44 hr. at room temperature, then with hot water. The precipitated solids were collected, dried, and purified from aqueous methanol, giving 3α : 12α-diacetoxytestan-17-one, m. p. and mixed m. p. 154—155°, $[\alpha]_D^{19}$ +171° (*c*, 0·838) (Found: C, 70·3; H, 8·7. Calc. for $C_{23}H_{34}O_5$: C, 70·8; H, 8·7%). The same compound was prepared from pregnane-3α : 12α : 17α : 20β-tetraol by oxidation with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371), followed by acetylation.

3α-*Ethoxycarbonyloxy-12α-hydroxypregnan-20-one* had m. p. 144° (from aqueous methanol), $[\alpha]_D^{25}$ +115° (*c*, 0·414) (Found: C, 70·9; H, 9·4. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·4%). The 12 : 20-*dione*, prepared from this (870 mg.; crude) in *tert.*-butanol (20 ml.) and water (4 ml.) with *N*-bromosuccinimide (600 mg.) overnight at room temperature, had m. p. 135°, $[\alpha]_D^{22\cdot5}$ +183° (*c*, 1·058) (Found: C, 71·8; H, 9·0. $C_{24}H_{36}O_5$ requires C, 71·3; H, 8·9%), after crystallisation from aqueous methanol.

3α-*Hydroxypregnane-12 : 20-dione*, prepared by treatment of 3α : 12α-dihydroxypregnan-20-one (1·66 g.) in acetic acid (45 ml.) with potassium chromate (1·74 g.) in water (4 ml.) at room temperature for 20 hr., had m. p. 149—151°, $[\alpha]_D^{23}$ +188° (*c*, 0·796) (Found: C, 76·0; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·6%), after purification from acetone–hexane. The *acetate* had m. p. 159—161°, $[\alpha]_D^{23}$ +193° (*c*, 0·564) (Found: C, 73·8; H, 9·0. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%).

3α : 12α-*Diacetoxy-20-ethoxypregn-17-ene* (XIII; R′ = OEt).—(i) (I) (1·7 g.) in ethanol (2·5 ml.) and ethyl orthoformate (1 ml.) containing concentrated sulphuric acid (1 drop) was heated under reflux for 30 min. Methanol (10 ml.) containing pyridine (1 drop) was added and the mixture left overnight at 0°. The separated solids were collected, washed with ice-cold methanol (yield 270 mg.; 15%), and purified from acetone–methanol. 3α : 12α-*Diacetoxy-20-ethoxypregn-17-ene* formed needles, m. p. 200—211°, $[\alpha]_D^{19}$ +140·8°, falling to +132·6° in 3½ hr. (*c*, 0·692) (Found: C, 73·0; H, 9·3. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·4%).

(ii) (I) (1 g.) in ethyl orthoformate (6 ml.) containing toluene-*p*-sulphonic acid (100 mg.) was heated under reflux for 1 hr., and the enol ether isolated as before (m. p. 190—194°; 120 mg., 11·4%).

12α : 17α-*Dihydroxypregnan-3 : 20-dione* (X; R = :O, R′ = H).—(i) 3α : 12α : 17α-Trihydroxypregnan-20-one (530 mg.) in *tert.*-butanol (10 ml.), pyridine (0·4 ml.), and water (0·4 ml.) was oxidised with *N*-bromoacetamide (370 mg., 1·75 mols.) at room temperature for 7 hr., giving 12α : 17α-*dihydroxypregnane-3 : 20-dione*, needles, m. p. 210—212°, $[\alpha]_D^{27}$ +71° (*c*, 0·404) (Found: C, 72·3; H, 9·3. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), after purification from acetone–hexane.

(ii) Trihydroxypregnanone (50 mg.) in *tert.*-butanol (4 ml.) and water (0·4 ml.) was oxidised with *N*-bromosuccinimide (56 mg.) at room temperature for 2 hr., giving the same dione.

The 12α-*acetate*, m. p. 105°, $[\alpha]_D^{27}$ +113° (*c*, 0·456) (Found : C, 70·4; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%), crystallised from acetone–hexane.

4β-*Bromo*-12α : 17α-*dihydroxypregnane*-3 : 20-*dione* (XII; R = R′ = H) was prepared by treatment of 12α : 17α-dihydroxypregnane-3 : 20-dione (340 mg.) in acetic acid (10 ml.) and hydrogen bromide (1 drop of 50% solution in acetic acid) with 0·985M-bromine–acetic acid (1·01 ml.) for 15 min. at room temperature. After crystallisation from acetone–hexane, it formed needles, m. p. 170—171° (decomp)., $[\alpha]_D^{23}$ +86° (*c*, 0·422) (Found : C, 61·0; H, 7·3; Br, 16·1. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·3; Br, 18·7%).

12α : 17α-*Dihydroxypregn*-4-*ene*-3 : 20-*dione* (XVI; R = R′ = H), prepared from the foregoing compound by dehydrobromination (with semicarbazide), formed needles, m. p. 224—226°, $[\alpha]_D^{22}$ +92° (*c*, 0·408), $\lambda_{max.}$ 240 mμ (log ε 4·28) (Found : C, 72·7; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), from acetone–hexane. The acetate separated from acetone–hexane in plates, m. p. 149°.

3α : 12α : 20ξ : 21-*Tetra-acetoxypregnane* (XV; R′ = Ac).—3α : 12α : 21-Triacetoxypregnan-20-one (1·5 g.) in ether (150 ml.) was added to lithium aluminium hydride (1·5 g.) in ether (100 ml.) which had been heated under reflux for 15 min. Heating was continued for 30 min. and the product, isolated with ethyl acetate, acetylated (acetic anhydride–pyridine, 15 : 20 ml., for 1 hr. at 100°) and chromatographed in benzene on alumina (40 g.). From the benzene to benzene–ether (70 : 30) eluates, 3α : 12α : 20ξ : 21-*tetra-acetoxypregnane* (30% yield) was obtained, forming needles, m. p. 131°, $[\alpha]_D^{20}$ +109° (*c*, 0·496) (Found : C, 66·7; H, 8·5. $C_{29}H_{44}O_8$ requires C, 66·9; H, 8·5%), from acetone–hexane.

Pregnane-3α : 12α : 20ξ : 21-*tetraol* (XV; R = α-OH, R′ = H), prepared by hydrolysis of the foregoing compound with methanolic sodium hydroxide, formed needles, m. p. 209—211°, $[\alpha]_D^{22}$ +101° (*c*, 0·442) (Found : C, 68·1; H, 10·4. $C_{21}H_{36}O_4,H_2O$ requires C, 68·1; H, 10·3%), from aqueous methanol.

Pregnane-3α : 12α : 17α : 20ξ : 21-*pentaol*, prepared by reduction of 3α : 12α : 21-triacetoxy-16α : 17α-epoxypregnan-20-one (1·6 g.) in ether (100 ml.) with lithium aluminium hydride (1·8 g.) in ether (180 ml.) for 2 hr. under reflux, formed needles, m. p. 262—263° (Found : C, 68·9; H, 9·7. $C_{21}H_{36}O_5$ requires C, 68·5; H, 9·8%), from methanol–ethyl acetate.

The *tetra-acetate* separated from acetone–hexane in crystals, m. p. 167—168° (Found : C, 64·9; H, 7·9. $C_{29}H_{44}O_9$ requires C, 64·9% H, 8·2%).

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Phthalaldehydes and Related Compounds. Part V. Phthalaldehydes derived from Hydrastal and Cotarnone.*

By John Blair and G. T. Newbold.

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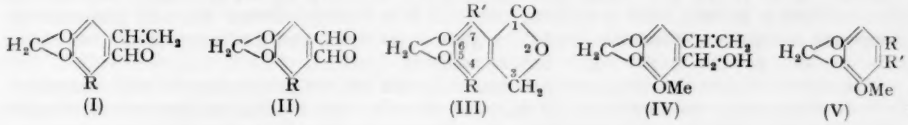
Hydrastal and cotarnone have been degraded to 4 : 5-methylenedioxyphthalaldehyde and its 3-methoxy-analogue respectively, and the action of alkali on the phthalaldehydes has been examined.

Hydrastal (I; R = H) was obtained as the end-product of a Hofmann elimination reaction applied to hydrastinine (Freund, *Ber.*, 1889, **22**, 2329) while cotarnone (I; R = OMe) resulted from the application of a similar process to cotarnine (Roser, *Annalen*, 1888, **249**, 156). We find that hydrastal is readily degraded to **4** : 5-methylenedioxyphthalaldehyde (II; R = H) by hydroxylation of the vinyl group by the osmium tetroxide method followed by periodate oxidation of the diol, which was not isolated. Treatment of (II; R = H) with concentrated aqueous potassium hydroxide gave **5** : 6-methylenedioxyphthalide (III; R = R′ = H) which has been prepared from homopiperonylic acid (Stevens, *J.*, 1927, 178; Stevens and Robertson, *ibid.*, p. 2790; Brown and Newbold, *J.*,

* Part IV, *J.*, 1954, 1076.

1952, 4397). Cotarnone is converted into 3-methoxy-4 : 5-methylenedioxyphthalaldehyde (II; R = OMe) either by the method used for hydrastal or more conveniently by ozonolysis at a low temperature. The phthalaldehyde (II; R = OMe) on being heated with concentrated aqueous alkali gave 4-methoxy-5 : 6-methylenedioxyphthalide (III; R = OMe, R′ = H) previously obtained by Späth, Schmid, and Sternberg (*Ber.*, 1934, **67**,



(I) (II) (III) (IV) (V)

2095) by the action of formaldehyde and hydrochloric acid on myristicinic acid (V; R = CO_2H, R′ = H). We have prepared the phthalide (III; R = OMe, R′ = H) by another route; reduction of cotarnone (I; R = OMe) with sodium borohydride gave 2-hydroxymethyl-3-methoxy-4 : 5-methylenedioxystyrene (IV); this compound was benzoylated and submitted to low-temperature ozonolysis and the product, not isolated, was treated with concentrated alkali, whereupon 4-methoxy-5 : 6-methylenedioxyphthalide (III; R = OMe, R′ = H) was readily obtained.

An attempt was made to prepare the isomeric phthalide, 7-methoxy-5 : 6-methylenedioxyphthalide (III; R = H, R′ = OMe). Myristicinic acid (V; R = CO_2H, R′ = H) was converted into methyl myristicinate (V; R = CO_2Me, R′ = H), nitration of which proceeded smoothly to give methyl 3-methoxy-4 : 5-methylenedioxy-2-nitrobenzoate (V; R = CO_2Me, R′ = NO_2) the orientation of the entering nitro-group being inferred from the nitration of ethyl myristicinate to (V; R = CO_2Et, R′ = NO_2) (Salway, *J.*, 1911, **99**, 266). Catalytic hydrogenation of (V; R = CO_2Me, R′ = NO_2) afforded methyl 2-amino-3-methoxy-4 : 5-methylenedioxybenzoate (V; R = CO_2Me, R′ = NH_2) which was smoothly reduced to 2-amino-3-methoxy-4 : 5-methylenedioxybenzyl alcohol (V; R = CH_2·OH, R′ = NH_2) by the action of lithium aluminium hydride. Attempts to convert (V; R = CH_2OH, R′ = NH_2) by the Sandmeyer reaction into the nitrile and to hydrolyse this to the isomeric methoxymethylenedioxyphthalide [lactone of (V; R = CH_2·OH, R′ = CO_2H)] were unsuccessful.

Experimental

Ultra-violet absorption spectra were determined in ethanol solution.

4 : 5-*Methylenedioxyphthalaldehyde*.—A solution of hydrastal (176 mg.; Brown and Newbold, *J.*, 1952, 4397) in dry benzene (25 c.c.) containing pyridine (0·16 c.c.) was treated with osmic acid (260 mg.), and the solution which darkened and soon began to deposit brown crystals was kept overnight at *ca.* 15°. The osmic acid–pyridine complex (450 mg.) was separated and heated under reflux in ethanol (30 c.c.) with sodium sulphite (5 g.) in water (20 c.c.) for 1 hr. Ethanol (150 c.c.) was added, the mixture filtered, and the solid extracted with boiling ethanol (2 × 30 c.c.). The combined ethanolic extracts were evaporated under reduced pressure, the residue was extracted with boiling methanol (2 × 50 c.c.) and the combined extracts were evaporated to a yellow gum. This was dissolved in pure methanol (3 c.c.), water (30 c.c.) and potassium periodate (1·0 g.) were added, the mixture was kept overnight, with occasional shaking, and extracted with ether (2 × 25 c.c.). The combined ethereal extracts were washed with water (25 c.c.) and dried (Na_2SO_4). Evaporation of the ether and crystallisation of the solid from benzene (charcoal) and benzene–light petroleum (b. p. 60—80°) gave 4 : 5-*methylenedioxyphthalaldehyde* (70 mg.) as pale yellow needles, m. p. 149—150° (Found: C, 60·8; H, 3·6. $C_9H_6O_4$ requires C, 60·7; H, 3·4%). Light absorption: Max. at 2500 (ε 26,200) and 3220 Å (ε 5300). The compound, suspended in aqueous ammonia (10%) and acidified with acetic acid, gave a violet solution (Thiele test, *Annalen*, 1900, **311**, 360).

5 : 6-*Methylenedioxyphthalide*.—4 : 5-Methylenedioxyphthalaldehyde (50 mg.) was heated on the steam-bath with potassium hydroxide (2 c.c.; 50%) for 15 min. The filtered solution was acidified (Congo-red) with 3N-hydrochloric acid, and the precipitate was separated and crystallised from aqueous ethanol, to give 5 : 6-methylenedioxyphthalide (20 mg.) as needles, m. p. 187—188° alone or mixed with a specimen prepared by Brown and Newbold (*loc. cit.*)

(Found: C, 60·5; H, 3·6. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·4%). Light absorption: Max. at 2210 (ε 23,000), 2560 (ε 5700), and 3000 Å (ε 7300).

Cotarninemethine Methiodide.—Cotarnine (4·0 g.) and methyl iodide (30 c.c.) were heated under reflux for 1 hr. and the excess of reagent was removed by distillation. Crystallisation of the residue from water gave cotarninemethine methiodide (70%) as needles, m. p. 217—218° (Found: C, 43·1; H, 5·3. Calc. for $C_{14}H_{20}O_4NI$: C, 42·8; H, 5·1%). Light absorption: Max. at 2180 (ε 26,600), 2420 (ε 22,100), and 2920 Å (ε 10,600). Roser (*loc. cit.*) prepared the compound but gave no constants though he gave an analysis, and Rodionow (*Bull. Soc. chim.*, 1926, **39**, 305) gave m. p. 219—220° but no analysis.

Cotarnone.—Roser (*loc. cit.*) gave insufficient details for the preparation of this compound. It is essential that our procedure be followed exactly. Pure cotarninemethine methiodide (15·0 g.) was rapidly heated with aqueous sodium hydroxide (250 c.c.; 10%) to the b. p., refluxed for 5 min., and then cooled. The oily phase rapidly solidified and was broken up, separated, washed with water, dried, and crystallised from light petroleum (b. p. 40—60°), to give cotarnone (6·2 g.) as plates, m. p. 78° (lit., 78°), giving a blue colour with acetic acid–sulphuric acid. Cotarnone had absorption max. at 2500 (ε 19,200) and 3020 Å (ε 6200).

3-*Methoxy*-4 : 5-*methylenedioxyphthalaldehyde.*—(*a*) A solution of cotarnone (810 mg.) in benzene (50 c.c.) containing pyridine (0·625 c.c.) was treated with osmic acid (1·0 g.) as given above for hydrastal, the complex was split, and the product oxidised with potassium periodate in aqueous methanol. 3-*Methoxy*-4 : 5-*methylenedioxyphthalaldehyde* (500 mg.), isolated by means of acid-free chloroform, separated from benzene as needles, m. p. 179° (Found: C, 57·5; H, 4·1. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%). Light absorption: Max. at 2560 (ε 26,900) and 3200 Å (ε 5900). The compound becomes brown on prolonged exposure to light.

(*b*) A solution of cotarnone (0·5 g.) in chloroform (200 c.c.) at −40° was treated with a stream of ozonised oxygen until 1 mol. of ozone had been absorbed. Water (10 c.c.) was added and the mixture heated to the b. p., with shaking, during 10 min. and refluxed for 15 min. The chloroform layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure to a solid which after two crystallisations from benzene gave 3-methoxy-4 : 5-methylenedioxyphthalaldehyde (250 mg.) as needles, m. p. and mixed m. p. with preparation (*a*), 179° (Found: C, 58·1; H, 4·2%).

2-*Hydroxymethyl*-3-*methoxy*-4 : 5-*methylenedioxystyrene.*—A solution of cotarnone (200 mg.) in ethanol (10 c.c.) and water (25 c.c.) was treated with sodium borohydride (500 mg.) and kept at *ca.* 15° overnight. The solution was extracted with chloroform (3 × 25 c.c.), and the combined extracts were washed with water (20 c.c.) and dried (Na_2SO_4). Removal of the chloroform gave an oil which was distilled in a short-path still at 200° (bath-temp.)/0·5 mm. The distillate, which rapidly solidified, crystallised from light petroleum (b. p. 40—60°) to give 2-*hydroxymethyl*-3-*methoxy*-4 : 5-*methylenedioxystyrene* (150 mg.) as needles, m. p. 47° (Found: C, 63·7; H, 6·1. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%). Light absorption: Max. at 2220 (ε 27,000) and 2700 Å (ε 9700). A solution of the compound in glacial acetic acid gave a red-brown colour on addition of sulphuric acid (*d* 1·84).

4-*Methoxy*-5 : 6-*methylenedioxyphthalide.*—(*a*) 3-Methoxy-4 : 5-methylenedioxyphthalaldehyde (300 mg.) was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for 1 hr. The cooled solution was extracted with ether (2 × 20 c.c.); evaporation of the combined, dried (Na_2SO_4) extracts gave a negligible residue. Acidification (Congo-red) of the aqueous phase with 3N-hydrochloric acid was followed by extraction with chloroform (3 × 35 c.c.). The combined chloroform extracts were washed with 10% aqueous sodium hydrogen carbonate and with water, dried (Na_2SO_4), and evaporated. The residue was twice crystallised from aqueous ethanol to give needles (171 mg.), m. p. 138—139° not rising on subsequent crystallisation. This material was heated at 100°/10^{-4} mm., partial sublimation taking place. Four crystallisations of the residue from aqueous ethanol gave 4-methoxy-5 : 6-methylenedioxyphthalide (50 mg.) as needles, m. p. 150—150·5° (Found: C, 58·05; H, 4·2. Calc. for $C_{10}H_8O_5$: C, 57·7; H, 3·9%). Light absorption: Max. at 2220 (ε 26,600) and 2730 (ε 7000) and inflexion at 2900—3000 Å (ε 4200). Späth, Schmid, and Sternberg (*loc. cit.*) give m. p. 150—151°.

(*b*) 2-Hydroxymethyl-3-methoxy-4 : 5-methylenedioxystyrene (600 mg.) was heated on the steam bath for ¾ hr. with benzoyl chloride (3 c.c.) and pyridine (5 c.c.), and the product was isolated by means of ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a viscous oil which was further purified by dissolving it in benzene (10 c.c.), adsorbing it on an alumina column (5 × 1·5 cm.), washing the column with benzene (200 c.c.), and evaporating the eluate to a colourless gum. The gum was dissolved in chloroform (150 c.c.) and treated

at −30° with ozonised oxygen (1·1 mols. of ozone) and worked up as for the previous ozonolysis, the aqueous phase giving the formaldehyde–dimedone compound, m. p. and mixed m. p. 190°. Removal of the chloroform gave a gum (which gave a precipitate, rapidly, with Brady's reagent) which was heated on the steam-bath with aqueous potassium hydroxide (30 c.c.; 40%) for ¾ hr., cooled, and extracted with ether. The aqueous phase was acidified (Congo-red) with 5N-hydrochloric acid, and the phthalide isolated by means of ether. Crystallisation from aqueous ethanol gave 4-methoxy-5 : 6-methylenedioxyphthalide (130 mg.) as needles, m. p. 151° alone or mixed with preparation (*a*) (Found: C, 57·6; H, 4·2%). Light absorption: Max. at 2230 (ε 26,500) and 2710 (ε 6600), inflexion at 2900—3000 Å (ε 4200).

Methyl Myristicinate.—Myristicinic acid (1·7 g.) in dry methanol (100 c.c.) containing sulphuric acid (4 c.c.; *d* 1·84) was heated under reflux for 2½ hr. The solution was concentrated to one-third of its volume under reduced pressure, then diluted with water, and the ester was isolated by means of chloroform. *Methyl myristicinate* (1·5 g.) separated from methanol as needles, m. p. 91° (Found: C, 57·1; H, 5·0. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%). Light absorption: Max. at 2230 (ε 19,900) and 2790 (ε 8100).

Methyl 3-Methoxy-4 : 5-methylenedioxy-2-nitrobenzoate.—Methyl myristicinate (1·13 g.) was added in portions to nitric acid (12 c.c.; *d* 1·42) cooled in ice at such a rate that the temperature did not rise above 10°. After 30 min. at 0° water (30 c.c.) was added, and the precipitate filtered off, washed with water, and crystallised from ethanol, to give *methyl 3-methoxy-4 : 5-methylenedioxy-2-nitrobenzoate* (1·0 g.) as needles, m. p. 127° (Found: C, 47·3; H, 3·85. $C_{10}H_9O_7N$ requires C, 47·1; H, 3·6%). Light absorption: Max. at 2230 (ε 28,000) and 2720 Å (ε 6300).

Methyl 2-Amino-3-methoxy-4 : 5-methylenedioxybenzoate.—The foregoing nitro-ester (960 mg.) in ethyl acetate (150 c.c.) was shaken with hydrogen in the presence of Raney nickel (0·4 g.; W6, prepared according to *Org. Synth.*, **29**, 25) until absorption ceased (2 hr.). The filtered solution was evaporated under reduced pressure and the residue crystallised from light petroleum (b. p. 60—80°) to give *methyl 2-amino-3-methoxy-4 : 5-methylenedioxybenzoate* (720 mg.) as needles, m. p. 89·5° (Found: C, 53·4; H, 4·7. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9%). Light absorption: Max. at 2260 (ε 23,000), 2690 (ε 5700), and 3660 Å (ε 6400).

2-Amino-3-methoxy-4 : 5-methylenedioxybenzyl Alcohol.—A solution of the amino-ester (610 mg.) in dry ether (10 c.c.) was added during 15 min. to a refluxing partial solution of lithium aluminium hydride (1·0 g.) in dry ether (40 c.c.). After 3 hours' refluxing the cooled mixture was treated with ice and made strongly alkaline with sodium hydroxide, and the ethereal phase was separated. After further extraction of the aqueous phase with ether (2 × 100 c.c.) the combined extracts were dried (Na_2SO_4) and evaporated to an oil which rapidly solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave *2-amino-3-methoxy-4 : 5-methylenedioxybenzyl alcohol* (470 mg.) as needles, m. p. 99° (Found: C, 55·0; H, 5·8. $C_9H_{11}O_4N$ requires C, 54·8; H, 5·6%). Light absorption: Max. at 2130 (ε 31,000 and 3000 (ε 3100); inflexion at 2420 Å (ε 5000). The compound sublimes rapidly at 80°/10^{-4} mm.

We are glad to acknowledge with thanks gifts of chemicals from Messrs. T. & H. Smith, Ltd.

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Kinetics and Mechanism of Side-chain Reactions in Some Substituted Phenethyl Chlorides and Benzyl Chlorides.

By Massimo Simonetta and Giorgio Favini.

[Reprint Order No. 4789.]

Hydrolysis rate constants have been determined in water–alcohol or water–acetone in the presence or absence of potassium hydroxide, for the following chlorides: Phenethyl, *o*-, *m*-, and *p*-methoxyphenethyl, benzyl, *o*-, *m*-, and *p*-methoxybenzyl. The mechanisms by which such molecules react in the various conditions have been identified as S_N1, S_N2, $E2$, and the values of the rate constants are correlated with the electronic concentration at the carbon atom to which the side chain is linked.

When the theory of the mechanism of nucleophilic substitution reactions at a saturated carbon atom, as developed by Ingold and Hughes (see Ingold, "Structure and Mechanism in Organic Chemistry," Chapter VII, Bell & Sons, Ltd., London, 1953), is applied to side-chain reactions in benzene derivatives, the influence of the various substituents in the benzene ring can be interpreted according to Hammett's σ-values ("Physical Organic Chemistry," Chapter VII, McGraw-Hill Book Co. Inc., New York, 1940). His theory has recently been discussed on a quantum-mechanical basis by Jaffé (*J. Chem. Phys.*, 1952, **20**, 279, 778, 1554; 1953, **21**, 415), who adopts the hypothesis that substituents in the *meta*- or *para*-position to a side chain in a compound affect the reaction of the side chain by virtue of their influence on the electron density of the reactive centre. The substituent changes the distribution of the π electrons in the benzene ring; the change in the charge on the carbon atom to which the side chain is bound is transmitted to the reactive centre in a manner dependent on the nature of the side chain, but the change itself is essentially independent of the nature of the side chain. It is possible in this way to correlate the rates of side-chain reactions with the electronic concentrations at the carbon atom to which the chain is linked.

As a first application to nucleophilic substitutions we consider the reaction between *o*-, *m*-, and *p*-methoxybenzyl chloride and water. (Hammett's theory refers to *meta*- and *para*-substituents only: here *ortho*-substituents are included, but steric effects or, more generally, *ortho*-effects must be taken into account.)

Since it is assumed that the variation in electronic concentration at the various points of the ring is independent of the nature of the side chain, we have calculated electron densities in the positions *ortho*, *meta*, and *para* to the methoxyl group in the anisole molecule. The calculation was performed according to Jaffé (*loc. cit.*, where values obtained for the hydroxyl group are indicated, which involve parameters with slightly different values), by the M.O. method in its standard L.C.A.O. approximation. The parameter values adopted were: 0·52 [in resonance integral for the carbon–carbon bond in benzene (β) units] for the Coulomb integral of the oxygen atom (α); 0·55 for the oxygen–carbon resonance integral (γ); $(1/3)^n\alpha$ for the Coulomb integrals of the carbon atoms separated from the oxygen atom by n bonds. We obtained the following values for the electronic densities (in electronic charge units):

ortho: 1·036 *meta*: 0·992 *para*: 1·017

Hammett's σ values for the methoxyl group are: $\sigma_m = +0{\cdot}115$; $\sigma_p = -0{\cdot}268$.

We measured the rate of the reaction of the corresponding benzyl chlorides with water; since the reactivity varies considerably from one compound to the other, we had to employ acetone–water mixtures of varying composition as solvents. The results are given in Table 1 (k_1 in hr.$^{-1}$). The velocity constants are not directly comparable owing to the different composition of the solvents: however, the reactivity of the compounds in solvolytic reactions is definitely in the order *para* > *ortho* > (unsubstituted) > *meta*, *i.e.*, the same order as the electronic concentration at the carbon atom to which the chain is linked, except for the *para*–*ortho* inversion due to steric effect.

The kinetics were strictly of the first order in all the experiments.

Benzyl chloride and its *meta*-substituted derivative were tested also in the presence of potassium hydroxide, but now the S_N1 mechanism was altered to $S_N2 + S_N1$. This is confirmed not only by the change in the order of the reaction but by a marked alteration in the velocity itself (*e.g.*, for benzyl chloride at 60° in aqueous alcohol the degree of hydrolysis rises from 10·55% in 2 hr. in the absence of alkali to 43·3% in 1 hr. in

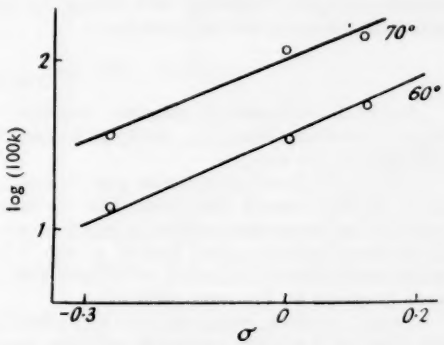
TABLE 1.

Compound	Solvent	k_1 at 60°	k_1 at 40°
p-Methoxybenzyl chloride	Acetone–water (5 : 1)	—	0·404
o- ,,	,, (5 : 1)	0·0378	—
	,, (2 : 1)	0·738	0·0924
Benzyl chloride	,, (2 : 1)	0·00684	—
m-Methoxybenzyl chloride	,, (2 : 1)	0·00459	—

the presence of 1 mol. of potassium hydroxide). Further, in the alkaline solution the difference between the rates of reaction of the two compounds is greatly diminished, and it is probable that if only the S_N2 mechanism operated the order of reactivity would be inverted. (Naturally, in aqueous alcoholic solutions the alcohol also has a solvolytic function.)

The log k against σ curve for the reaction between methoxyphenethyl chlorides and potassium hydroxide in aqueous alcohol.

$\rho_{70°} = 0{\cdot}0156$
$\rho_{60°} = 0{\cdot}0164$



We next examined the reactions of methoxy-substituted phenethyl chlorides with potassium hydroxide in aqueous solution. The process is complicated, since substitution takes place simultaneously with elimination: furthermore, the styrenes so formed may polymerise, thus complicating the process.

It must be borne in mind that the methoxy-group may also be hydrolysed, but conductometric analyses of the solutions and of specimen solutions of phenol–anisole mixtures indicated that this process was inappreciable. By determining the ionisable chlorine by titration with silver nitrate we were able to calculate constants for the combined $S_N2 + E2$ reactions; in an attempt to obtain the separate constants, we determined the olefins present in the solution at the various times, but this failed, probably because the polymerisation processes affected the quantity of determinable double bonds. It is therefore desirable that these velocities of polymerisation be determined and we are endeavouring to do this. Furthermore, unlike the process with benzyl derivatives, there is no agreement between the values of chloride ion as determined by Volhard's method and acidimetrically; the latter values also do not permit calculation of the total constants, probably because the base is involved in secondary reactions. On the other hand, the total constants obtained by the other method are very good; on the whole, the reactions are of second order and agree with the $S_N2 + E2$ mechanism.

The values of the constants (k_2 in hr.$^{-1}$ mole^{-1} l.) are indicated in Table 2 [chloro-derivative 0·1N; KOH, 0·1N in ethyl alcohol–water (2 : 1)]. They agree excellently with the theory (apart from the usual *ortho–para* inversion). The data for the non-substituted compound can be used in conjunction with the graph above to work out the values of Hammett's ρ constant for the whole reaction in our experimental conditions.

We have also measured the velocity at which chloride ion is formed at 95° in the absence of potassium hydroxide (again in ethyl alcohol–water, 2 : 1); the following are the values of the constants k_1 (in hr.$^{-1}$): Phenethyl chloride, 0·0034; *p*-methoxyphenethyl chloride,

TABLE 2.

	At 60°	At 70°		At 60°	At 70°
Phenethyl chloride	0·340	1·080	*m*-Methoxyphenethyl chloride	0·510	1·410
o-Methoxyphenethyl chloride...	0·0725	0·224	*p*- ,,	0·125	0·370

0·0105. It is apparent that in passing from the S_N2 to the S_N1 mechanism the order of reactivity between the two compounds is inverted, while at the same time the velocity of reaction is greatly diminished. Therefore both benzyl and the phenethyl derivatives can give rise to chloride ions by both mechanisms, the single-stage and the two-stage.

Baddeley and Bennett's results (*J.*, 1935, 1819) on bimolecular reaction with potassium iodide in acetone seem partly to conflict with the data and the interpretation given above. At 75° these authors found the following values for k_2 (in hr.$^{-1}$ mole^{-1} l.): Phenethyl chloride, 0·735; *p*-methoxyphenethyl chloride, 1·040. This might be a case of bimolecular reaction where the predominating factor is the fission of the existing bond instead of the formation of the new bond. Before advancing this or any other explanation, however, we intend to repeat Baddeley and Bennett's experiments and to extend them to the *meta*- and *ortho*-substituted compounds.

EXPERIMENTAL

Materials.—Phenethyl chloride, prepared by chlorination of 1-phenylpropan-1-ol with thionyl chloride (Ward, *J.*, 1927, 453) and dried (K_2CO_3), was fractionally distilled; it had b. p. 83—84°/14 mm.

o-Methoxyphenethyl chloride was obtained from the corresponding alcohol by chlorination as for the *meta*-isomer (Bergmann and Weizmann, *J. Org. Chem.*, 1939, **4**, 266). The alcohol, prepared by interaction of the Grignard reagent from *o*-bromoanisole with an ice-cold solution of ethylene oxide in ether, had b. p. 135°/13 mm., and the chloride had b. p. 117°/20 mm. *m*-Methoxyphenethyl chloride, b. p. 122—123°/18 mm., and the *para*-isomer, b. p. 130°/20 mm., were prepared by the same method.

Benzyl chloride, obtained from a commercial sample by distillation, had b. p. 77°/20 mm., n_D^{15} 1·54148. *o*-Methoxybenzyl chloride was prepared as follows: Salicylaldehyde was methylated with methyl sulphate in presence of alkali (Hell and Hofmann, *Ber.*, 1905, **38**, 1676), the *o*-methoxybenzaldehyde was treated with alkali, methanol, and formaldehyde (Davidson and Bogert, *J. Amer. Chem. Soc.*, 1935, **57**, 905), the resulting alcohol was chlorinated with thionyl chloride in presence of pyridine, and the chloro-compound was purified by distillation: it had b. p. 108°/15 mm.

The same procedure was followed in the preparation of the *para*-isomer from anisaldehyde: from the alcohol (a white solid, m. p. 23°) by chlorination we got *p*-methoxybenzyl chloride, b. p. 120°/20 mm. (Found: Cl, 22·3. Calc. for $C_8H_7O_2Cl$: Cl, 22·4%). The *meta*-isomer was prepared from *m*-hydroxybenzaldehyde by methylation, reduction, and chlorination as for the *ortho*-isomer. The aldehyde was obtained from *m*-nitrobenzaldehyde by reduction, diazotisation, and hydrolysis (Woodward, *Org. Synth.*, **25**, 55). *m*-Methoxybenzyl chloride had b. p. 124°/13 mm. (Found: Cl, 22·2%).

Acetone was purified by Conant and Kirner's method (*J. Amer. Chem. Soc.*, 1924, **46**, 245) and fractionated. Commercial absolute alcohol was dried by Smith's method (*J.*, 1927, 1288) as modified by Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1106) and fractionated.

Kinetic Measurements.—For the reactions with water or potassium hydroxide a known amount of the organic compound was dissolved in alcohol or acetone, and the solution was made up to volume. In each experiment appropriate volumes of the organic solution and of standard potassium hydroxide at the required reaction temperature were mixed so that the final mixture was 0·1N with respect to the organic compound; the time of mixing was taken as the zero time for reaction. The thermostats were steady to within 0·05°. After known times samples of 25 ml. were withdrawn.

(i) When the solute was a phenethyl chloride the sample was added to 20 ml. of 0·3N-nitric acid. After titration of the acidity with 0·1N-potassium hydroxide in presence of phenolphthalein and acidification with dilute nitric acid the solution was shaken with 50 ml. of carbon

tetrachloride, and the organic layer was washed with water and used for the determination of olefin by Hughes and Shapiro's method (*J.*, 1937, 1192); the aqueous layer and the water used in washing the organic layer were used for determination of chloride ion (Volhard).

TABLE 3.

0·1N-Phenethyl chloride with 0·1N-KOH in ethyl alcohol–water (2 : 1) at 70°.

t (hr.)	1	2	3	4	5	6	7	8
Cl–	2·52	4·13	6·30	7·55	8·73	9·72	10·37	11·02
Olefin	10·95	14·02	15·55	17·13	28·95	32·53	35·20	40·25
k_2	1·120	0·990	1·120	1·080	1·070	1·060	1·010	0·985

0·1N-*o*-Methoxybenzyl chloride in acetone–water (2 : 1) at 50°.

t (min.)	0	30	60	120	180
KOH	0·739	4·164	6·649	10·760	13·480
k_1	—	0·3036	0·2790	0·2670	0·2700
$AgNO_3$	0·850	4·077	6·612	10·997	14·354
k_1	—	0·2850	0·2718	0·2712	0·2730

0·1N-Benzyl chloride in ethyl alcohol–water (2 : 1) at 70°.

t (min.)	0	150	180	240	300
KOH	0·335	7·645	8·887	11·130	12·900
k_1	—	0·140	0·142	0·144	0·142
$AgNO_3$	0·350	7·675	8·839	11·120	12·867
k_1	—	0·141	0·141	0·144	0·144

TABLE 4. *Benzyl chloride derivatives* (0·1N).

Substituent	Solvent	Temp.	k_1	E_a	Substituent	Solvent	Temp.	k_1	E_a
o-OMe	$COMe_2$–H_2O (2 : 1)	40°	0·0924	20·600	(H)	EtOH–H_2O (2 : 1)	60°	0·0560	21·100
		50	0·275				70	0·142	
		60	0·738		(H)	$COMe_2$–H_2O (2 : 1)	60	0·00684	—
p-OMe	$COMe_2$–H_2O (5 : 1)	20	0·0535	18·300	*m*-OMe	$COMe_2$–H_2O (2 : 1)	60	0·00459	—
		30	0·156		*o*-OMe	$COMe_2$–H_2O (5 : 1)	60	0·0378	—
		40	0·404						
m-OMe	$COMe_2$–H_2O (1 : 1)	40	0·00295	19·550	(H)	EtOH–H_2O * (2 : 1)	60	7·20 †	—
		50	0·00840		*m*-OMe	EtOH–H_2O * (2 : 1)	60	5·70 †	—
		60	0·0205						

* With addition of 0·1N-KOH. † Values are those of k_2.

TABLE 5. *Phenethyl chloride derivatives* (0·1N) *with* 0·1N-KOH *in alcohol–water* (2 : 1).

Substituent	Temp.	k_2	E_a	Substituent	Temp.	k_2	E_a	Substituent	Temp.	k_2	E_a
(H)	50°	0·118	24·800	*p*-OMe	60°	0·124	24·600	*m*-OMe	60°	0·510	23·020
	55	0·205			70	0·370			70	1·410	
	60	0·340		*o*-OMe	60	0·0725	25·350	(H)	95	0·0033 *	—
	65	0·588			70	0·224		*p*-OMe	95	0·0105 *	—
	70	1·080									

* KOH was omitted in these experiments and values are those of k_1.

(ii) When the solutes were benzyl chlorides the sample was added to 25 ml. of carbon tetrachloride; after shaking and removal of the organic layer, the aqueous layer was washed with a further 10 ml. of carbon tetrachloride, diluted with water, and titrated first with 0·1N-potassium hydroxide, and then, after acidification with dilute nitric acid, with silver nitrate. (Reaction mixtures containing potassium hydroxide were not titrated for acidity.)

In the annexed record of our experiments, the amount of chloride ion present in the sample is expressed in ml. of 0·1N-silver nitrate or potassium hydroxide, and the olefin in ml. of 0·02N-sodium thiosulphate; k_1 (in hr.$^{-1}$) and k_2 (in hr.$^{-1}$ mole^{-1} l.) are first- and second-order rate coefficients. A few typical runs are given in Table 3, and Tables 4 and 5 summarise the results.

Inverse Reactions.—50 ml. of a 0·12N-solution of *p*-methoxybenzyl alcohol in acetone were treated with 10 ml. of 0·6N-hydrochloric acid for 4 hr. at 40°; 25 ml. of the mixture needed 24·37 ml. of 0·1N-silver nitrate at the beginning and 24·27 ml. at the end of the reaction.

40 ml. of a 0·15N-solution of *o*-methoxybenzyl alcohol in acetone were treated with 20 ml. of

0·3N-hydrochloric acid for 15·5 hr. at 60°; titration at the beginning, 24·03 ml. of 0·1N-silver nitrate, and at the end 24·01 ml.

30 ml. of a 0·2N-solution of *m*-methoxybenzoyl alcohol in acetone were treated with 30 ml. of 0·2N-hydrochloric acid for 8 hr. at 60°; the titration as above were 25·3 and 25·2 ml., respectively.

Reaction Products.—5·95 g. of *o*-methoxybenzyl chloride in 100 ml. of acetone and 50 ml. of water were heated at 60° for 5 hr. After neutralisation, the acetone and the water were removed under vacuum, the residue was dissolved in ether, the solution filtered from the potassium chloride, and the ether removed. By distillation of the residue 3·5 g. of o-methoxybenzyl alcohol were obtained (b. p. 128°/20 mm.; n_D^{17} 1·54973). Similarly, 2·375 g. of *p*-methoxybenzyl chloride in 50 ml. of acetone and 25 ml. of water at 40° for 5 hr. gave 1·5 g. of the corresponding alcohol (b. p. 135—140°/20 mm.; n_D^{15} 1·5479), and 2·28 g. of the *meta*-isomer in 50 ml. of acetone and 50 ml. of water at 60° for 40 hr. gave 1 g. of the benzyl alcohol (b. p. 141°/25 mm.; n_D^{28} 1·55418).

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Synthesis of β-Amino-sulphones and αβ-Unsaturated Sulphones.

By M. BALASUBRAMANIAN and V. BALIAH.

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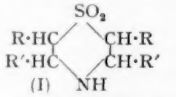
Arylsulphonylacetic acids have been condensed with aldehydes and bases. A number of *N*-substituted 2-aminoalkyl aryl sulphones (II) and 1-aryl-2-arylsulphonylethylenes (III) have been obtained. *p*-Tolylsulphonylacetic acid condenses with chloral, to give 3 : 3 : 3-trichloro-2-hydroxypropyl *p*-tolyl sulphone (IV).

THE activating influence of a sulphonyl group on the hydrogen atoms attached to the adjacent carbon atom has been studied by a number of workers (see Suter, " The Organic Chemistry of Sulphur," Wiley, New York, 1944, p. 687; Gilman, " Organic Chemistry," Wiley, New York, 1943, p. 879). Most of the reactions involving activation by a sulphonyl group are undergone by alkyl- or aryl-sulphonylacetic acids, their derivatives, and keto-sulphones and disulphones. The Mannich reaction has not been applied to compounds containing reactive hydrogen atoms in a $\cdot CH_2 \cdot SO_2R$ group: Chodroff and Whitmore (*J. Amer. Chem. Soc.*, 1950, **72**, 1073) attempted to apply it to a series of α-arylsulphonyl-alkanecarboxylic acids in the presence of diethylamine but isolated only unsaturated sulphones of the type $C_6H_5 \cdot SO_2 \cdot CR{:}CH_2$. Having in view the somewhat similar condensations with ketones, aldehydes, and bases studied by Noller and Baliah (*ibid.*, 1948, **70**, 3853) we attempted to condense dimethyl, diethyl, dipropyl, and dibutyl sulphones with benzaldehyde and ammonia or amines to get compounds of the type (I), but failed. Benzyl phenyl sulphone and di- and tri-phenylsulphonylmethane also failed to condense. However, we found that arylsulphonylacetic acids undergo this type of reaction. Phenyl- and *p*-tolyl-sulphonylacetic acid condensed with aromatic aldehydes and ammonia or aliphatic primary amines to give the β-amino-sulphones (II), decarboxylation occurring during the reaction. Simultaneously αβ-unsaturated sulphones (III) were formed.



(I) $R \cdot SO_2 \cdot CH_2 \cdot CHR' \cdot NHR''$ (II) $R \cdot SO_2 \cdot CH{:}CHR'$ (III)

The reaction was carried out by refluxing the reagents in glacial acetic acid solution for 5—15 minutes. Longer times resulted in a lower yield of the amino-sulphone and a corresponding increase in the yield of the unsaturated sulphone. The latter type was produced exclusively when *p*-tolylsulphonylacetic acid was heated with benzaldehyde and ammonia in glacial acetic acid for 40 minutes; this suggests that the amino-sulphone initially formed decomposed to the unsaturated sulphone: indeed, 2-amino-2-phenylethyl *p*-tolyl sulphone, heated in glacial acetic acid under reflux for 30 minutes, gave 1-phenyl-2-*p*-tolyl-sulphonylethylene.

The condensation seems to be limited to aromatic aldehydes. Aliphatic aldehydes such as formaldehyde, acetaldehyde, and *n*- and *iso*-butyraldehyde failed to condense with *p*-tolylsulphonylacetic acid and ammonia. However, chloral underwent an aldol condensation :

$$p\text{-Me}\cdot C_6H_4\cdot SO_2\cdot CH_2\cdot CO_2H + CCl_3\cdot CHO \longrightarrow p\text{-Me}\cdot C_6H_4\cdot SO_2\cdot CH_2\cdot CH(OH)\cdot CCl_3 \quad (IV)$$

Of amines, ammonia and aliphatic primary amines condensed readily, but secondary amines failed to condense. For example, a mixture of *p*-tolylsulphonylacetic acid, benzaldehyde, and piperidine in acetic acid gave only 1-phenyl-2-*p*-tolylsulphonylethylene. When diethylamine was used in the place of piperidine, *p*-tolylsulphonylacetic acid was decarboxylated to methyl *p*-tolyl sulphone.

When arylsulphonylalkanecarboxylic acids are used in the place of arylsulphonylacetic acids, the condensation appears to proceed less readily; *e.g.*, α-*p*-tolylsulphonylpropionic acid condensed with ammonia and benzaldehyde or *m*-nitrobenzaldehyde only after 1 hour's refluxing. The yields were also poor in these cases.

Experimental

Triphenylsulphonylmethane.—Diphenylsulphonylmethane (Shriner, Struck, and Jorison, *J. Amer. Chem. Soc.*, 1930, **52**, 2060) (4·2 g.) and phenyl benzenethiolsulphonate (3·6 g.) were added to a solution obtained by dissolving sodium (0·4 g.) in ethanol (40 c.c.). The mixture was heated on a water-bath under reflux for 6 hr., poured into water (150 c.c.), and made alkaline with 10% sodium hydroxide solution. After removal of alkali-insoluble matter by ether, the solution was acidified with hydrochloric acid. The precipitated phenylthiobisphenylsulphonylmethane (3·8 g.) was obtained as colourless needles (from glacial acetic acid), m. p. 177·5—178·5°. Oxidation of this compound with hydrogen peroxide (30%) in acetic acid gave triphenylsulphonylmethane (64%), m. p. 215—217° (from acetic acid) (cf. Laves, *Ber.*, 1892, **25**, 347).

Condensation of Arylsulphonylacetic Acids with Aldehydes and Amines.—In general, a mixture of the arylsulphonylacetic acid (0·02 mole), the aldehyde (0·02 mole), and ammonium acetate or the aliphatic amine (0·02 mole) in glacial acetic acid (4 c.c.) was heated under reflux for 5—15 min. The reaction was stopped after the brisk evolution of carbon dioxide subsided. The resulting solution was cooled, mixed with ether (50 c.c.), and set aside for 1 hr. The ethereal layer was removed and on passage of dry hydrogen chloride into it, the β-amino-sulphone hydrochloride was obtained as needles either immediately or on short standing. In certain cases even a slight excess of hydrogen chloride coloured the product yellow or brown, and so the hydrochloride was precipitated by addition of sufficient ether saturated with hydrogen chloride. After complete separation of the hydrochloride (1—2 days), it was filtered off (filtrate A) and washed with ether and then with acetone. Crystallisation from ethanol or ethanol–ether gave needles. The data relating to these *hydrochlorides* are recorded in Table 1.

The αβ-unsaturated sulphone was obtained from the filtrate A. Evaporation of the ether left a residue which was a mixture of unchanged aldehyde, acetic acid, and unsaturated sulphone. Almost pure crystals of the last were obtained by shaking this mixture with a few c.c. of methanol. Crystallisation from ethanol or methanol gave the analytical sample.

The unsaturated sulphones derived from *m*-nitrobenzaldehyde were insoluble in ether. In these cases, after the addition of ether to the reaction mixture, the precipitated unsaturated sulphone was filtered off, and the filtrate treated as usual with hydrogen chloride to give the β-amino-sulphone hydrochloride. The unsaturated *sulphones* are listed in Table 2.

p-*Tolyl* 3 : 3 : 3-*Trichloro*-2-*hydroxypropyl Sulphone.*—A mixture of *p*-tolylsulphonylacetic acid (4·28 g.), ammonium acetate (1·54 g.), chloral (2·86 g.), and glacial acetic acid (4 c.c.) was heated under reflux for 30 min. The resulting brown solution was dissolved in ether (60 c.c.) and saturated with hydrogen chloride. The ammonium chloride that separated was filtered off. Removal of ether from the filtrate gave a liquid which gradually yielded crystals of the *sulphone*; colourless rhombic crystals (0·72 g.), m. p. 127—129° (Found : C, 37·9; H, 3·3. $C_{10}H_{11}O_3Cl_3S$ requires C, 37·8; H, 3·5%), were obtained from benzene.

2-*Amino*-1-*methyl*-2-*phenylethyl* p-*Tolyl Sulphone Hydrochloride.*—To a solution of α-*p*-tolylsulphonylpropionic acid (Chodroff and Whitmore, *loc. cit.*) (2·28 g.) and benzaldehyde (1·06 g.) in acetic acid (2 c.c.), ammonium acetate (0·77 g.) was added, and the mixture heated under reflux for 1 hr. After cooling, the product was extracted with ether and the *hydrochloride* (0·22 g., 7%) was precipitated. It was filtered off (filtrate B) and crystallised from ethanol–

TABLE 1. *β-Amino-sulphone hydrochlorides*, $R{\cdot}SO_2{\cdot}CH_2{\cdot}CHR'{\cdot}NHR'',HCl$.

No.	R′	R″	M. p.	Yield (%) [a]	Formula	Found, % C	H	Cl⁻	Required, % C	H	Cl⁻
				R = Phenyl.							
1	Ph	H	190—193°	27(21)	$C_{14}H_{15}O_2NS,HCl$	56·2	5·7	12·0	56·5	5·4	11·9
2	3 : 4-$(CH_2O_2)C_6H_3$	H	213—215(d)	30(19)	$C_{15}H_{15}O_4NS,HCl$	52·6	5·1	10·4	52·7	4·7	10·4
3	*o*-MeO·C_6H_4	H	211—213	20(28)	$C_{15}H_{17}O_3NS,HCl$	54·6	5·6	10·8	55·0	5·5	10·8
4	*p*-C_6H_4Cl	H	213—215	24(28)	$C_{14}H_{14}O_2NClS,HCl$	50·6	4·3	10·7	50·6	4·5	10·7
5	*o*-$NO_2{\cdot}C_6H_4$	H	225—228(d)	7(10)	$C_{14}H_{14}O_4N_2S,HCl$	49·4	4·5	10·4	49·1	4·4	10·4
6	*m*-$NO_2{\cdot}C_6H_4$	H	217—219	21(14)	$C_{14}H_{14}O_4N_2S,HCl$	48·8	4·6	10·2	49·1	4·4	10·4
7	2-Thienyl	H	210—212(d)	14 [a]	$C_{12}H_{13}O_2NS_2,HCl$	47·6	4·9	12·0	47·5	4·6	11·7
8	Ph	CH_2Ph	179—181	10(27)	$C_{21}H_{21}O_2NS,HCl$	64·9	5·5	9·4	65·0	5·7	9·2
9	*p*-C_6H_4Me	—	—	(17) [b]	—	—	—	—	—	—	—
				R = *p*-Tolyl.							
10	Ph	H	204—206	23(25)	$C_{15}H_{17}O_2NS,HCl$	58·1	5·6	11·3	57·8	5·8	11·4
11	3 : 4-$(CH_2O_2)C_6H_3$	H	213—214(d)	22(15)	$C_{16}H_{17}O_4NS,HCl$	53·8	5·1	10·1	54·0	5·0	10·0
12	*o*-MeO·C_6H_4	H	220—222	19(23)	$C_{16}H_{19}O_3NS,HCl$	56·1	6·0	10·6	56·2	5·8	10·4
13	*p*-MeO·C_6H_4	H	231—232	19(12)	$C_{16}H_{19}O_3NS,HCl$	56·0	6·1	10·6	56·2	5·8	10·4
14	*p*-C_6H_4Cl	H	206—209	19(31)	$C_{15}H_{16}O_2NClS,HCl$	52·1	5·2	10·2	51·9	4·9	10·2
15	*o*-$NO_2{\cdot}C_6H_4$	H	237—239(d)	18(5)	$C_{15}H_{16}O_4N_2S,HCl$	50·2	5·1	10·0	50·5	4·8	10·0
16	*m*-$NO_2{\cdot}C_6H_4$	H	219—220	25(20)	$C_{15}H_{16}O_4N_2S,HCl$	—	—	10·3	—	—	10·0
17	*p*-C_6H_4Me	H	195—197·5	25(22)	$C_{16}H_{19}O_2NS,HCl$	59·0	6·3	11·1	59·0	6·1	10·9
18	2-Thienyl	H	196·5—198·5(d)	15(20)	$C_{13}H_{15}O_2NS_2,HCl$	49·4	5·3	11·2	49·1	5·0	11·2
19	Ph	Me	185—188	8(35)	$C_{16}H_{19}O_2NS,HCl$	58·8	5·7	10·8	59·0	6·1	10·9
20	*m*-$NO_2{\cdot}C_6H_4$	Me	203—205	30(48)	$C_{16}H_{18}O_4N_2S,HCl$	—	—	9·4	—	—	9·6
21	Ph	Et	199—200	21(54)	$C_{17}H_{21}O_2NS,HCl$	60·1	6·7	10·6	60·1	6·5	10·4
22	*m*-$NO_2{\cdot}C_6H_4$	Et	208—210	23(41)	$C_{17}H_{20}O_4N_2S,HCl$	53·0	5·8	9·0	53·1	5·5	9·0
23	Ph	Allyl	177—178·5	13(43)	$C_{18}H_{21}O_2NS,HCl$	61·5	6·3	10·4	61·5	6·3	10·1
24	*m*-$NO_2{\cdot}C_6H_4$	Allyl	210—213	33(62)	$C_{18}H_{20}O_4N_2S,HCl$	54·5	4·9	9·1	54·5	5·3	8·9
25	Ph	Bu	185—188	9(60)	$C_{19}H_{25}O_2NS,HCl$	61·9	7·1	9·9	62·0	7·1	9·6
26	*m*-$NO_2{\cdot}C_6H_4$	Bu	195—198	14(70)	$C_{19}H_{24}O_4N_2S,HCl$	55·5	6·2	8·6	55·3	6·1	8·6
27	Ph	Octyl	169—171	11(61)	$C_{23}H_{33}O_2NS,HCl$	65·0	8·3	8·4	65·2	8·0	8·4
28	*m*-$NO_2{\cdot}C_6H_4$	Octyl	197—199	19(53)	$C_{23}H_{32}O_4N_2S,HCl$	58·7	6·6	7·6	58·9	7·0	7·6
29	Ph	CH_2Ph	194—195·5	36(64)	$C_{22}H_{23}O_2NS,HCl$	65·6	6·2	8·9	65·8	6·0	8·8
30	3 : 4-$(CH_2O_2)C_6H_3$	CH_2Ph	205—206	27(30)	$C_{23}H_{23}O_4NS,HCl$	61·8	5·4	8·3	61·9	5·4	8·0
31	*m*-$NO_2{\cdot}C_6H_4$	CH_2Ph	207—209·5	10(56)	$C_{22}H_{22}O_4N_2S,HCl$	59·2	5·2	8·0	59·1	5·2	7·9

[a] The percentage yields in parentheses are those of the αβ-unsaturated sulphones. The bases corresponding to Nos. 4, 16, and 20 were obtained by treatment of the corresponding hydrochlorides with aqueous ammonia in ethanol. *Base* from No. 4, colourless needles (ethanol–water), m. p. 98—99° (Found: C, 57·0; H, 5·0. $C_{14}H_{14}O_2NClS$ requires C, 56·9; H, 4·7%). *Base* from No. 16, yellow needles (methanol–water), m. p. 97—98° (Found: C, 56·3; H, 4·9. $C_{15}H_{14}O_4N_2S$ requires C, 56·3; H, 5·0%). *Base* from No. 20, colourless prisms (methanol), m. p. 108·5—109·5° (Found: C, 57·4; H, 5·4. $C_{16}H_{18}O_4N_2S$ requires C, 57·5; H, 5·4%).

[a] No unsaturated compound could be isolated. [b] No Mannich base could be isolated. (d) M. p. with decomp.

TABLE 2. *αβ-Unsaturated sulphones*, $R{\cdot}SO_2{\cdot}CH{:}CHR'$.

R′	M. p.	Formula	Found, % C	H	Required, % C	H
	R = Ph.					
Ph	74—74·5° [a]	$C_{14}H_{12}O_2S$	68·7	4·6	68·9	4·9
3 : 4-$(CH_2O_2)C_6H_3$	107—108	$C_{15}H_{12}O_4S$	62·4	4·5	62·5	4·2
o-MeO·C_6H_4	93—94	$C_{15}H_{14}O_3S$	65·6	4·9	65·7	5·1
p-ClC_6H_4	129·5—130	$C_{14}H_{11}O_2ClS$	60·3	4·2	60·3	4·0
o-$NO_2{\cdot}C_6H_4$	130—132	$C_{14}H_{11}O_4NS$	58·4	3·8	58·1	3·8
m-$NO_2{\cdot}C_6H_4$	145—146	$C_{14}H_{11}O_4NS$	57·8	4·1	58·1	3·8
p-C_6H_4Me	135·5—136·5	$C_{15}H_{14}O_2S$	70·1	5·6	69·8	5·4
	R = *p*-Tolyl.					
Ph	120·5—121 [b]	$C_{15}H_{14}O_2S$	69·8	5·4	69·8	5·4
3 : 4-$(CH_2O_2)C_6H_3$	114—114·5	$C_{16}H_{14}O_4S$	63·6	4·5	63·6	4·6
o-MeO·C_6H_4	81—82	$C_{16}H_{16}O_3S$	66·8	5·6	66·7	5·6
p-MeO·C_6H_4	100 (softens 88)	$C_{16}H_{16}O_3S$	66·4	5·6	66·7	5·6
p-$C_6H_4{\cdot}Cl$	151—153	$C_{15}H_{13}O_2ClS$	61·6	4·5	61·6	4·4
o-$NO_2{\cdot}C_6H_4$	158·5—160	$C_{15}H_{13}O_4NS$	59·3	4·5	59·4	4·3
m-$NO_2{\cdot}C_6H_4$	146—147	$C_{15}H_{13}O_4NS$	59·3	4·3	59·4	4·3
p-$C_6H_4{\cdot}Me$	154—155	$C_{16}H_{16}O_2S$	70·4	5·6	70·6	5·9
2-Thienyl	132·5—133·5	$C_{13}H_{12}O_2S_2$	59·4	4·7	59·1	4·6

[a] Field (*J. Amer. Chem. Soc.*, 1952, **74**, 3919) gives m. p. 74—75°. [b] Chodroff and Whitmore (*loc. cit.*) record m. p. 119·5—120°; Kohler and Potter (*J. Amer. Chem. Soc.*, 1935, **57**, 1316) give m. p. 121°.

ether as needles, m. p. 235—240° (decomp.) (Found: C, 58·9; H, 6·4; Cl^-, 10·9. $C_{16}H_{19}O_2NS,HCl$ requires C, 59·0; H, 6·3; Cl^-, 10·9%). Evaporation of the filtrate B yielded 1-*methyl*-2-*phenyl*-1-p-*tolylsulphonylethylene* (0·32 g., 11·8%), m. p. 118·5—119·5° (from ethanol) (Found: C, 70·5; H, 5·9. $C_{16}H_{16}O_2S$ requires C, 70·6; H, 5·9%).

2-*Amino*-1-*methyl*-2-m-*nitrophenylethyl* p-*Tolyl Sulphone Hydrochloride*.—By the same procedure as above, a mixture of α-*p*-tolylsulphonylpropionic acid (2·28 g.), *m*-nitrobenzaldehyde (1·51 g.), ammonium acetate (0·77 g.), and glacial acetic acid (2 c.c.) afforded the *hydrochloride* named (0·59 g., 16%), needles, m. p. 245—254° (decomp.) (from ethanol) (Found: C, 52·0; H, 5·3; Cl^-, 9·5. $C_{16}H_{19}O_4N_2S,HCl$ requires C, 51·8; H, 5·1; Cl^-, 9·6%). The ethereal solution gave 1-*methyl*-2-m-*nitrophenyl*-1-p-*tolylsulphonylethylene* (0·31 g., 10%), pale yellow plates (from methanol), m. p. 132—133° (Found: C, 60·4; H, 4·8. $C_{16}H_{15}O_4NS$ requires C, 60·6; H, 4·7%).

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pseudo*Carpaine, a New Alkaloid from* Carica papaya *L.*

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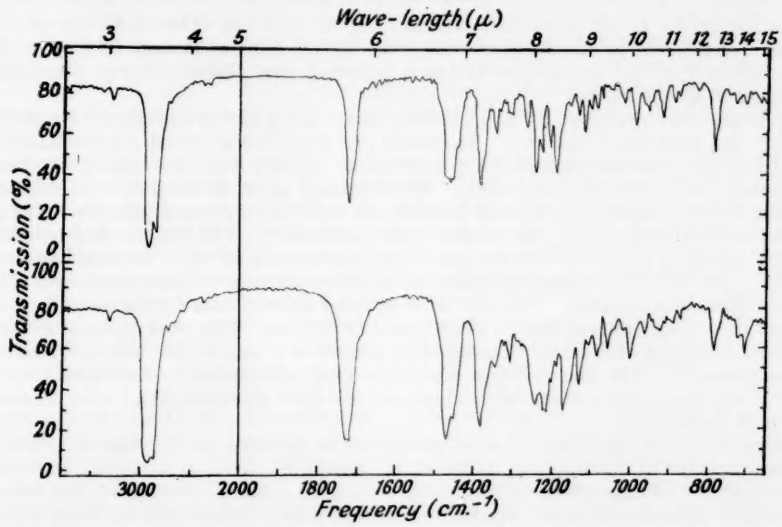
The leaves of *Carica papaya* L. are shown to contain a new alkaloid, *pseudo*carpaine, isomeric with carpaine. Evidence is presented that *pseudo*-carpaine differs from carpaine only in the configuration at the "alcoholic" carbon atom.

THE alkaloid carpaine, first isolated by Greshoff (*Ber.*, 1890, **23**, 3537) from the leaves of *Carica papaya* L., is the only alkaloid reported from this source. Recently, we had occasion to process a fair amount of papaya leaves for isolation of carpaine. Previous

Infra-red absorption spectra of carpaine (top) and pseudo*carpaine (bottom), in Nujol mull.*

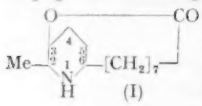


workers (Barger, Girardet, and Robinson, *Helv. Chim. Acta*, 1933, **16**, 90; Barger, Robinson, and Work, *J.*, 1937, 711; Rapaport and Baldridge, *J. Amer. Chem. Soc.*, 1951, **73**, 343), except Greshoff (*loc. cit.*), had isolated carpaine in yields ranging from 0·018 to 0·04%: we have obtained it in 0·11% yield. In addition, we isolated, in 0·01% yield, an alkaloid to which we assign the name *pseudo*carpaine. The new alkaloid has the same molecular formula as carpaine, $C_{14}H_{25}O_2N$, but differs from it in melting point, rotation,

and solubility characteristics. The infra-red absorption spectra are very similar (see Figure), notable differences being found only in the 7—15 μ region.

Dehydrogenation of *pseudo*carpaine in *p*-cymene with palladised charcoal yielded 2 mols. of hydrogen and deoxycarpyrinic acid, identical with that obtained from carpaine (Rapaport and Baldridge, *J. Amer. Chem. Soc.*, 1952, **74**, 5365) under the same conditions. Hydrolysis of *pseudo*carpaine with concentrated hydrochloric acid gave an amino-acid in quantitative yield; this material, isolated as the hydrochloride, did not melt sharply and attempts to obtain sharp-melting fractions from what was evidently a mixture, by repeated crystallisations, did not succeed. The product was esterified by the Fischer procedure. Crystallisation of the ester hydrochloride yielded a first fraction (*ca.* 50%), consisting of ethyl carpamate hydrochloride, and a second fraction of ethyl *pseudo*carpamate hydrochloride. Dehydrogenation of the latter ester yielded ethyl carpyrinate (Govindachari and Narasimhan, *J.*, 1953, 2635). Reduction of *pseudo*carpaine with lithium aluminium hydride yielded *pseudo*carpamodiol, $C_{14}H_{29}O_2N$, isomeric with carpamodiol obtained by reduction of carpaine with the same reagent (Govindachari and Narasimhan, *loc. cit.*).

Carpaine yields on hydrolysis a single product, carpamic acid, in quantitative yield. Rapaport, Baldridge, and Volcheck (*J. Amer. Chem. Soc.*, 1953, **75**, 5290) have shown conclusively that carpaine has structure (I). Hydrolysis of *pseudo*carpaine to both *pseudo*carpamic and carpamic acid shows that *pseudo*carpaine is diastereoisomeric with carpaine, differing only in configuration at $C_{(3)}$. It may be that carpaine undergoes hydrolysis solely by acyl–oxygen fission, whereas *pseudo*carpaine undergoes hydrolysis at least partly by alkyl–oxygen fission with formation of $C_{(3)}$-epimers, steric factors being responsible for this difference.



(I)

Reduction with lithium aluminium hydride yields a single product in each case as expected, there being no change in the configuration at $C_{(3)}$ during lactone cleavage by this reagent.

Experimental

Isolation of the Crude Alkaloids.—Papaya leaves were collected from the districts of Mangalore and Salem in Madras State and from the environs of Madras City. The highest alkaloid content (0·2%) was present in leaves collected from Malaya, though *pseudo*carpaine was present in all the sources.

The leaves were extracted by the following procedure which is considerably simpler than Rapaport and Baldridge's (*loc. cit.*). The dried, powdered leaves (14 kg.; from Malaya) were covered with 90% alcohol containing 1% acetic acid. After 3 days, the extract was drawn off. The material was extracted twice more. The combined alcoholic extracts were concentrated to a small volume, initially at ordinary pressure and later under reduced pressure. The residue was treated with water (3 l.), and acidified with acetic acid. The mixture was shaken intermittently during 2 days and the aqueous layer was poured off from the non-basic resinous material. The residue was again treated with further quantities of dilute acetic acid till it was free from alkaloidal material. The combined aqueous extracts were concentrated to about 2 l. *in vacuo*, cooled, and filtered from a small quantity of resin. The clear aqueous solution was repeatedly extracted with ether. The aqueous solution was then cooled well and basified with aqueous ammonia. The liberated base was thoroughly extracted with ether and, after drying (Na_2SO_4), and evaporation of the ethereal extract, the total alkaloids (28 g.) were obtained as a sticky light brown solid.

Separation of the Alkaloids.—The crude alkaloidal material (28 g.) was dissolved in the minimum amount of acetone and cooled at 0° overnight. The crystals that had separated were filtered off and constituted pure carpaine (12 g.), m. p. 121°. The filtrate was mixed with benzene and washed with water repeatedly. It was then extracted several times with dilute acetic acid. The acid extract was shaken with benzene to remove non-basic material, and rendered alkaline with sodium carbonate. The liberated base was extracted with benzene. Removal of the solvent after drying yielded 10·8 g. of a sticky oil. This was chromatographed in benzene on alumina (200 g.), the following fractions (total, 7·38 g.) being obtained: (i) by benzene (5 l.), a solid (3·6 g.; 3·1 g. thereof had m. p. 80—100°); (ii) by benzene + 1% of alcohol (5 l.), an oil (3·3 g.); and (iii) by benzene + 2·5% of alcohol (3·5 l.), an oil (0·48 g.). Fraction (i), after one crystallisation from acetone, gave pure carpaine (2·1 g.), m. p. 121°;

$[\alpha]_D^{28}$ +21·4° (*c*, 1·08 in EtOH). Fraction (ii), dissolved in absolute ether, was saturated with dry hydrogen chloride. The hydrochloride (2·1 g.) which was precipitated melted at 270—280°. Crystallisation from absolute alcohol yielded pure pseudo*carpaine hydrochloride* (1·4 g.), m. p. 295° (Found: C, 61·0; H, 9·5; N, 5·0. $C_{14}H_{26}O_2NCl$ requires C, 61·0; H, 9·4; N, 5·1%). A further crop of this hydrochloride (0·25 g.) was obtained from the mother-liquor after addition of absolute ether to turbidity. *pseudo*Carpaine hydrochloride was much less soluble in absolute alcohol than carpaine hydrochloride.

pseudo*Carpaine*, obtained by basification of an aqueous solution of the hydrochloride and extraction with ether, crystallised from light petroleum (b. p. 50—55°) and melted at 65—68°, $[\alpha]_D^{28}$ +4·95° (*c*, 1·62 in EtOH) (Found: C, 70·4; H, 10·4; N, 5·7. $C_{14}H_{25}O_2N$ requires C, 70·3; H, 10·5; N, 5·7%).

Dehydrogenation of pseudo*Carpaine*.—A solution of *pseudo*carpaine (200 mg.) in *p*-cymene was dehydrogenated by Rapaport and Baldridge's procedure (*loc. cit.*); 180 mg. of deoxycarpyrinic acid hydrochloride were obtained. Crystallisation from acetone gave colourless crystals, m. p. 74—76° (Found: C, 58·0; H, 8·2; N, 4·8. $C_{14}H_{22}O_2NCl,H_2O$ requires C, 58·0; H, 8·3; N, 4·8%).

Dehydrogenation of carpaine yielded the same hydrochloride, m. p. 74—76° alone or mixed with the above product.

Rapaport and Baldridge have isolated deoxycarpyrinic acid hydrochloride in the anhydrous form, m. p. 96—97°. Our product has the same ultra-violet absorption spectrum as that reported for deoxycarpyrinic acid hydrochloride by these authors.

Hydrolysis of pseudo*Carpaine*.—*pseudo*Carpaine hydrochloride (500 mg.) in concentrated hydrochloric acid (25 ml.) was refluxed for 4 hr. The solution was then evaporated to dryness *in vacuo*. The residue, thoroughly dried and crystallised from absolute alcohol–ether, furnished a hydrochloride (390 mg.), m. p. 133—145°; repeated crystallisation yielded material melting in the same range.

Esterification of the Hydrolysis Product.—A solution of the foregoing hydrochloride (390 mg.) in absolute alcohol (50 ml.) was saturated at 0° with dry hydrogen chloride. After being kept for 2 days, the solution was concentrated to 5 ml. Absolute ether was added to incipient turbidity. Overnight, a colourless crystalline hydrochloride (150 mg.) separated, melting at 160—170°, which on one crystallisation from alcohol–ether furnished ethyl carpamate hydrochloride, m. p. and mixed m. p. 173° (Found: C, 59·3; H, 9·4; N, 4·5. $C_{16}H_{32}O_3NCl$ requires C, 59·7; H, 10·0; N, 4·4%). The mother-liquor was evaporated to dryness and the resulting material, after decolorisation with charcoal, was crystallised from absolute alcohol–ether (180 mg.; m. p. 110—120°). One recrystallisation from absolute alcohol–ether furnished *ethyl* pseudo*carpamate hydrochloride*, m. p. 122—124° (Found: C, 60·0; H, 10·4; N, 4·3. $C_{16}H_{32}O_3NCl$ requires C, 59·7; H, 10·0; N, 4·4%).

Dehydrogenation of Ethyl pseudo*Carpamate*.—Ethyl *pseudo*carpamate (200 mg.) was dehydrogenated in *p*-cymene with 30% palladised charcoal (100 mg.). In 1 hr. hydrogen corresponding to 3 mols. was evolved. The dehydrogenation product isolated in the usual way melted at 78—80° and did not depress the melting point of ethyl carpyrinate.

pseudo*Carpamodiol*.—*pseudo*Carpaine (600 mg.) was reduced with lithium aluminium hydride, and the product was isolated as in the case of carpaine (Govindachari and Narasimhan *loc. cit.*). The oil (600 mg.) obtained initially gradually set to a solid. Two crystallisations from absolute ether gave pseudo*carpamodiol*, m. p. 78—80° $[\alpha]_D^{28}$ −13·53° (*c*, 2·18 in EtOH) (Found: C, 69·0; H, 12·0; N, 5·7. $C_{14}H_{29}O_2N$ requires C, 69·1; H, 12·0; N, 5·8%). Carpamodiol (Govindachari and Narasimhan, *loc. cit.*) had $[\alpha]_D^{28}$ −1·11° (*c*, 2·2 in EtOH).

Some analyses are by Mr. Selvavinayagam. We are grateful to Professor Roger Adams, University of Illinois, for the infra-red absorption spectra, to Mr. R. Peter for valuable help in extraction of the leaves, to Miss Uma Sundari for a supply of papaya leaves from Malaya, and to the Honorary Director, Indigenous Drugs Research Committee, the Vice-Principal, College of Indigenous Medicine, and the Government of Madras, for the award of a scholarship to one of us (N. S. N.).

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Reaction of Diazomethane with Arylideneanilines.

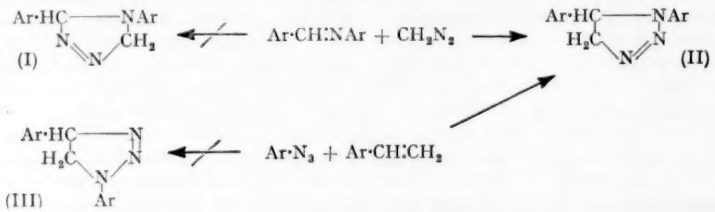
By G. D. Buckley.

[Reprint Order No. 5089.]

The compound obtained by the action of diazomethane on *p*-nitro-*N*-*p*′-nitrobenzylideneaniline is identical with the product of the reaction of *p*-nitrophenyl azide with *p*-nitrostyrene, and is therefore a 1 : 5-diaryl-1 : 2 : 3-triazoline.

Benzylideneaniline and *p*-chlorobenzylideneaniline with ethereal diazomethane in presence of methanol give 1 : 2 : 3-triazolines in 10—15% yield but do not react in absence of methanol.

Mustafa (*J.*, 1949, 234) has shown that certain nitro-derivatives of benzylideneaniline react with diazomethane to form heterocyclic compounds, to which he ascribes a 4 : 5-diaryl-1 : 2 : 4-triazoline structure (I) on very inadequate grounds. If Mustafa is correct the methylene group of the diazomethane has become attached to the nitrogen atom of the arylideneaniline, but this is unlikely because diazomethane normally reacts in the form $\bar{C}H_2\text{–}\overset{+}{N}\equiv N$ (cf. addition to carbonyl compounds), and in nucleophilic additions to the C=N bond the anion invariably becomes attached to the carbon atom (cf. addition of sodium cyanide, nitromethane, sodium hydrogen sulphite, etc.). It therefore seems probable that in the addition of diazomethane to arylideneanilines the methylene group will become attached to carbon rather than nitrogen, and the product will be a 1 : 5-diaryl-1 : 2 : 3-triazoline (II).



The structure of the product from diazomethane and *p*-nitro-*N*-*p*′-nitrobenzylideneaniline has been investigated. This compound must be either 4 : 5-di-*p*-nitrophenyl-1 : 2 : 4-triazoline (as I) or 1 : 5-di-*p*-nitrophenyl-1 : 2 : 3-triazoline (as II). 1 : 5-Diphenyl-1 : 2 : 3-triazoline (II; Ar = Ph) is formed by the action of phenyl azide on styrene (Wolff, *Annalen*, 1912, **394**, 68). *p*-Nitrophenyl azide was therefore treated with *p*-nitrostyrene in an attempt to synthesise (II; Ar = *p*-NO_2·C_6H_4). An addition product of empirical formula $C_{14}H_{11}O_4N_5$, which must be either (II or less probably III; Ar = *p*-NO_2·C_6H_4), was isolated. It was identical in melting point and infra-red spectrum with the compound obtained from diazomethane and the anil and must therefore be (II; Ar = *p*-NO_2·C_6H_4).

Formula (II) was rejected by Mustafa chiefly because he found that the compound dissociated to diazomethane and the anil at 270° and he considered it unlikely that the C–C bond in the 1 : 2 : 3-triazoline ring could be disrupted so easily. This is not, however, a valid objection since it has been shown that an analogous dissociation of the 1 : 2 : 3-oxadiazolines to diazomethane and a carbonyl compound may occur at 250° (Bridson-Jones, Buckley, Cross, and Driver, *J.*, 1951, 2999).

Mustafa (*loc. cit.*) reported that benzylideneaniline failed to react with ethereal diazomethane at 0°, and this has been confirmed. However, the addition of a little methanol to the mixture caused reaction to take place, and after ten days about 15% of the anil had been converted into 1 : 5 diphenyl-1 : 2 : 3-triazoline (II; Ar = Ph), which was identified by comparison with a specimen prepared by the action of phenyl azide on styrene. *p*-Chlorobenzylideneaniline reacted similarly with diazomethane in presence,

but not in absence, of methanol to give 5-*p*-chlorophenyl-1-phenyl-1 : 2 : 3-triazoline in small yield.

Experimental

Microanalyses are by Dr. A. F. Colson. M. p.s are corrected.

1 : 5-*Di*-(p-*nitrophenyl*)-1 : 2 : 3-*triazoline*.—(*a*) *p*-Nitro-*p'*-nitrobenzylideneaniline (2 g.) was finely powdered and added to an ice-cold solution of diazomethane (4 g.) in ether (100 c.c.). The mixture was held at 0° for 10 days, and the crystals (2·1 g.) were collected and washed with ether. Recrystallisation from ethyl acetate gave faintly yellow needles of 1 : 5-*di*-(p-*nitrophenyl*)-1 : 2 : 3-*triazoline*, m. p. 178° (decomp.) (Found: C, 53·6; H, 3·4; N, 22·2. $C_{14}H_{11}O_4N_5$ requires C, 53·65; H, 3·5; N, 22·35%).

(*b*) A mixture of *p*-nitrophenyl azide (3 g.), *p*-nitrostyrene (3 g.), and ethyl acetate (10 c.c.) was refluxed on a steam-bath for 4 hr. After the mixture had been cooled, the crystalline product (1·1 g.) was collected and washed with ethanol. Recrystallisation from ethyl acetate gave pale yellow crystals, m. p. 177° (decomp.) (Found: C, 53·6; H, 3·4; N, 22·6. Calc. for $C_{14}H_{11}O_4N_5$: C, 53·65; H, 3·5; N, 22·35%). Its infra-red absorption spectrum was identical with that of a specimen prepared by method (*a*).

1 : 5-*Diphenyl*-1 : 2 : 3-*triazoline*.—(*a*) A solution of benzylideneaniline (2 g.) in methanol (10 c.c.) was added to an ice-cold solution of diazomethane (4 g.) in ether (100 c.c.) and held at 0° for 10 days. The solvents were then allowed to evaporate at 20°, and the residue was extracted with 50 c.c. of cold ligroin (b. p. 40—60°). The insoluble material (0·25 g.) was collected and washed with ligroin. A duplicate experiment gave 0·3 g. Crystallisation from methanol gave colourless needles of 1 : 5-diphenyl-1 : 2 : 3-triazoline, m. p. 128° (decomp.) (Found: C, 75·2; H, 5·7; N, 18·8. Calc. for $C_{14}H_{13}N_3$: C, 75·3; H, 5·85; N, 18·85%).

(*b*) A mixture of phenyl azide (10 g.), styrene (9·3 g.), and ethyl acetate (20 c.c.) was refluxed on a steam-bath for 4 hr. The ethyl acetate was removed by distillation under reduced pressure. The residue, which partly crystallised on cooling, was treated with a little methanol and the crystals (2·4 g.) were collected. Recrystallisation from methanol gave colourless needles, m. p. 128° (decomp.), undepressed on admixture with a specimen prepared by method (*a*) (Found: C, 75·05; H, 5·7; N, 18·9. Calc. for $C_{14}H_{13}N_3$: C, 75·3; H, 5·85; N, 18·85%).

5-p-*Chlorophenyl*-1-*phenyl*-1 : 2 : 3-*triazoline*.—*p*-Chlorobenzylideneaniline (2 g.) was treated with diazomethane, as described above for benzylideneaniline. After removal of the ether and extraction of the residue with cold ligroin, crude 5-p-*chlorophenyl*-1-*phenyl*-1 : 2 : 3-*triazoline* (0·2 g.) was collected. Crystallisation from methanol gave colourless crystals, m. p. 128° (decomp. *ca.* 145°) (Found: N, 16·2; Cl, 13·2. $C_{14}H_{12}N_3Cl$ requires N, 16·3; Cl, 13·4%).

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Winnington, Northwich, Cheshire. [*Received, February 3rd*, 1954.]

Solutions in Sulphuric Acid. Part XVI. A Reconsideration of the Value of the Cryoscopic Constant.*

By R. J. Gillespie.

[Reprint Order No. 4888.]

It is shown that the cryoscopic constant k_f of sulphuric acid as defined in Part I (*J.*, 1950, 2473) is independent of the nature and concentration of any solute. A revised value of 6·12 is proposed. It is shown that Wyatt's claim (*J.*, 1953, 1175) that the cryoscopic constant varies with the nature and concentration of any solute results from a different, and it is believed less convenient, definition of this quantity.

Recently new data on the heat of fusion of sulphuric acid have been published (Rubin and Giauque, *J. Amer. Chem. Soc.*, 1952, **74**, 800), and Wyatt (*J.*, 1953, 1175) has criticised the value of the cryoscopic constant used in previous parts of this series (*e.g.*, Part I, *loc. cit.*), suggesting that this constant varies with the composition of the sulphuric acid

* Part XV, *J.*, 1954, 7.

solvent and with the nature and concentration of any solute. The value and exact significance of this quantity are reconsidered.

If the standard state of the solvent is chosen to be the pure liquid solvent and if a_s is the activity of the solid at temperature T

$$\mathrm{d} \ln a_s/\mathrm{d}T = \Delta H^f/\boldsymbol{R}T^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ΔH^f is the heat of fusion of the pure solvent at the temperature T (see Lewis and Randall, "Thermodynamics," McGraw-Hill, 1923, p. 282). Now for a *solution* at its freezing point T the activity of the liquid solvent a_1 is equal to the activity of the pure solid solvent a_s and hence

$$\mathrm{d} \ln a_1/\mathrm{d}T = \Delta H^f/\boldsymbol{R}T^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ΔH^f refers, as before, to the pure solid solvent melting to the pure liquid solvent at the temperature T and is *not* the total heat change accompanying the fusion of the pure solid when it melts into the solution as was assumed by Wyatt (*loc. cit.*). This can be understood because the activity of the solvent in solution is equal to the activity of the pure solid phase with which it is in equilibrium, and the activity of the pure solid is determined only by the properties of the pure substance and not by those of the solution. Allowing for the variation of the heat of fusion with temperature and by integrating equation (2) we obtain

$$\ln a_1 = \frac{-1}{\boldsymbol{R}T_0^2}\left[\Delta H_0{}^f\theta + \left(\frac{\Delta H_0{}^f}{T_0} - \frac{\Delta C_p}{2}\right)\theta^2 + \text{- - -}\right] \quad . \quad . \quad . \quad . \quad (3)$$

where $\Delta H_0{}^f$ is the heat of fusion of the pure solid solvent at the freezing point T_0 of the pure solvent, θ is the freezing point depression and ΔC_p is the difference between the heat capacities of the liquid and solid solvent (cf. Lewis and Randall, *op. cit.*). If the solution is ideal $a_1 = N_1$ and also

$$N_1 = [m_1 - s_2m_2]/[m_1 + (\nu_2 - s_2)m_2]$$

where m_1 is the molality of the solvent, m_2 the molality of the solute, s_2 the total number of solvent molecules required to react with the solute and to solvate the ions thus formed, and ν_2 is the number of ions formed. Substitution in equation (3) leads to

$$\frac{\Delta\theta}{\Delta m_2} = \nu_2\frac{\boldsymbol{R}T_0^2}{m_1\Delta H_0{}^f}\left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0{}^f}\right)\bar{\theta}\right\}\cdot\left\{1 + \frac{(2s_2 - \nu_2)\bar{m}_2}{m_1}\right\} \quad . \quad . \quad (4)$$

where $\bar{\theta}$ is the mean freezing point depression and $\bar{m}_2$ the mean molality of the solute (Part I, *loc. cit.*). The factor $\boldsymbol{R}T_0^2/m_1\Delta H_0{}^f$ is a constant of the solvent called the cryoscopic constant k_f. Hence

$$\frac{\Delta\theta}{\Delta m_2} = \nu_2k_f\left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0{}^f}\right)\bar{\theta}\right\}\cdot\left\{1 + \frac{(2s_2 - \nu_2)\bar{m}_2}{m_1}\right\} \quad . \quad . \quad . \quad (5)$$

From this definition, the cryoscopic constant must be constant under all conditions and independent of the nature and concentration of any solutes, provided that the solid phase is the pure solid solvent.

The accurate determination by Rubin and Giauque (*loc. cit.*) of the heat of fusion of sulphuric acid, $\Delta H_0{}^f = 2560$ cals., enables one to calculate the value of 6·12 for the cryoscopic constant. This value is definitely to be preferred to the value of 5·98 used previously in this series. This was a mean value determined from many cryoscopic measurements, since at that time (cf. Part I, *loc. cit.*), no accurate value for the heat of fusion of sulphuric acid was available.

Our definition and value of the cryoscopic constant are independent of the assumption of ideality made in deducing the above equations. If it is desired to allow for non-ideality of the solution this can be done most simply by introducing g, the rational osmotic

coefficient of the solvent at the freezing point *of the solution*, and writing $\ln a_1 = g \ln N_1$ which leads to

$$g \ln N_1 = -\left[\Delta H_0^f \theta + \left(\frac{\Delta H_0^f}{T_0} - \frac{\Delta C_p}{2}\right)\theta^2 + \cdots\right] \Big/ RT_0^2 \quad . \quad . \quad . \quad (6)$$

and

$$\frac{\Delta\theta}{\Delta m_2} = g\nu_2 k_f \left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0^f}\right)\bar{\theta}\right\} \cdot \left\{1 + \frac{(2s_2 - \nu_2)\bar{m}_2}{m_1}\right\} \quad . \quad . \quad . \quad (7)$$

or, if it is wished to make solvation part of the general non-ideality and thus assume for simplicity that $s_2 = 0$, this reduces to

$$\frac{\Delta\theta}{\Delta m_2} = g\nu_2 k_f \left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0^f}\right)\bar{\theta}\right\} \cdot \left\{1 - \frac{\nu_2\bar{m}_2}{m_1}\right\} \quad . \quad . \quad . \quad . \quad (8)$$

Wyatt defined the cryoscopic constant as $RT^2/(m_1 \Delta H'_f)$ where $\Delta H'_f$ is "the heat which is absorbed when 1 mole of the solvent passes from the solid phase into the liquid," which is equal to the sum of the heat of fusion of the pure solid and the partial molar heat of mixing of the pure liquid with the solution. We will denote this cryoscopic constant by k'_f to distinguish it from k_f defined by equations (4) and (5); k'_f will necessarily vary with the composition of the solution because of changes in the partial molar heat of mixing. For an ideal solution the two cryoscopic constants become identical because the heat of mixing is zero. For a non-ideal solution Wyatt's definition of the cryoscopic constant leads to the following equation

$$\frac{\Delta\theta}{\Delta m_2} = g'\nu_2 k'_f \left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0}\right)\bar{\theta}\right\} \cdot \left\{1 - \frac{\nu_2\bar{m}_2}{m_1}\right\} \quad . \quad . \quad . \quad . \quad (9)$$

which is similar to equation (8) except that k'_f replaces k_f and g', the osmotic coefficient at the freezing-point *of the pure solvent*, replaces g. This equation has the apparent advantage of giving the osmotic coefficient at a constant temperature, namely the freezing-point of the pure solvent, rather than at the freezing-point of the solution, but it has the serious disadvantage that unless the heat of mixing is known k'_f is unknown and therefore g' cannot be calculated. While it cannot be said that k'_f as defined by Wyatt is incorrect it would seem that k_f as defined by equations (4) and (5) is more useful and therefore to be preferred. Both equations (8) and (9) may be written:

$$\frac{\Delta\theta}{\Delta m_2} = \nu_2 k_{ap} \left\{1 - \left(\frac{2}{T_0} - \frac{\Delta C_p}{\Delta H_0}\right)\bar{\theta}\right\} \left\{1 - \frac{\nu_2\bar{m}_2}{m_1}\right\} \quad . \quad . \quad . \quad . \quad (10)$$

where $k_{ap} = gk_f = g'k'_f$ may be called the "apparent cryoscopic constant." Since k_{ap} can be experimentally determined and since k_f is known, g can always be calculated. On the other hand, since in general neither g' nor k'_f is known neither can be calculated.

It is incorrect to attempt, as Wyatt has done, to interpret any observed variations in the apparent cryoscopic constant k_{ap} entirely in terms of variations in k'_f. This implies that g' is unity which can only be the case if the solution is ideal and k_{ap} is therefore constant.

The variations of the apparent cryoscopic constant observed experimentally by Wyatt may be given simple alternative explanations. In oleum solutions the apparent cryoscopic constant calculated from the freezing-point depression produced by 2 : 4 : 6-trinitrotoluene was found to be less than 6·12 and to decrease with increasing sulphur trioxide concentration in the oleum. 2 : 4 : 6-Trinitrotoluene probably behaves as a weak base (Gillespie, *J.*, 1950, 2542); hence it will partially ionise: $B + H_3SO_4^+ = BH^+ + H_2SO_4$. This does not increase the total number of solute particles and therefore 2 : 4 : 6-trinitrotoluene gives a smaller depression than the ideal value in oleum solutions. As the strength of the oleum is increased the apparent cryoscopic constant would be expected to decrease further because of the increased ionisation of 2 : 4 : 6-trinitrotoluene and also the presence in the oleum of an increasing concentration of polysulphuric acids (Gillespie, *J.*, 1950, 2516). In aqueous sulphuric acid the apparent cryoscopic constant was found to be greater then 6·12 and to increase with increasing water concentration. This may reasonably be attributed to the slight basic ionisation of the solutes used (2 : 4 : 6-trinitrotoluene

and nitromethane) and to the neglect in the calculations of the effect of the ionisation and the solvation of the water on the mole fraction of the sulphuric acid.

When, as with sulphuric acid, the pure solvent is self-dissociated all the equations derived above and the definition of the cryoscopic constant k_f are still valid, and the osmotic coefficients that one obtains refer, as is usual, to the pure solvent as the standard state. However, where the added solute represses the self-dissociation of the solvent it may sometimes be more convenient to use instead of the pure solvent as the standard state a hypothetical non-dissociated solvent, or a hypothetical solvent that is dissociated to a different extent from the pure solvent. This is effectively what Wyatt has done in writing the heat of fusion term in the cryoscopic constant in the form $\Delta H_*^f + x\Delta H_d$ where ΔH_*^f is the heat of fusion of the hypothetical undissociated solvent, ΔH_d the heat of self-dissociation and x the degree of self-dissociation. This implies that the standard state is a hypothetical solvent in which the extent of self-dissociation is the same as that in the solution under consideration. It is less convenient to use this varying standard state but nevertheless in interpreting osmotic coefficients it may be preferable, particularly in the limiting case when sufficient solute is present to repress almost completely the self-dissociation.

Fortunately it is likely that for sulphuric acid it makes little practical difference which standard state is chosen. Thus Gillespie and Wasif (*J.*, 1953, 964) calculated that the heat of dissociation of sulphuric acid is approximately 2000 cals., and since x is approximately 0·002, $x\Delta H_d$ is approximately 4 cals., which is of the same order of magnitude as the experimental error in the heat of fusion ($\pm$3 cals.), and may therefore be neglected.

In nitric acid however, where the self-dissociation is much more extensive, it is important to select carefully the standard state and this question will be fully discussed in forthcoming papers on cryoscopic measurements in nitric acid.

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Researches on Acetylenic Compounds. Part XLII. Reductions with Lithium Aluminium Hydride.*

By E. B. Bates, E. R. H. Jones, and M. C. Whiting.

[Reprint Order No. 4926.]

Lithium aluminium hydride acts as a highly selective reducing agent toward acetylenic alcohols and glycols of various types. The steric configurations of the ethylenic products are discussed; *trans*-forms appear to be produced invariably. A number of spectrographic correlations are described.

The reduction of cinnamic acid and of cinnamaldehyde either to 3-phenylpropyl alcohol or, under milder conditions, to cinnamyl alcohol (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197, 2548; Hochstein and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3484) suggested that acetylenic compounds might similarly undergo partial or complete reduction at the triple bond when treated with lithium aluminium hydride. Such reductions have now been found to occur.

With an excess of the reagent at 20°, phenylpropiolic ester was converted essentially into cinnamyl alcohol; when the reactants were mixed at −70°, the product consisted essentially of phenylpropargyl alcohol. Benedict and Russell (*J. Amer. Chem. Soc.*, 1951, **73**, 5444) have described similar reactions with acetylenedicarboxylic and propiolic acids; see also Micovic and Mikhailovic (*Glasnik Chem. Drushty*, 1951, **16**, 19).

1-Ethynyl*cyclo*hexene was unaffected by the reagent in boiling ether, but gave a mixture of unsaturated hydrocarbons in dioxan at the boiling point. Similarly vigorous conditions gave the vinyl compound from 1-ethynyl*cyclo*hexanol, while a larger excess of reagent and

* Part XLI, *J.*, 1954, 147.

a longer reaction period gave 1-ethyl*cyclo*hexanol. 1-Phenylprop-2-yn-1-ol, on the other hand, gave the vinyl compound in 94% yield at 34°.

These reactions lack preparative interest, and hence were not studied intensively; they did, however, suggest that hydroxyl groups adjacent to the acetylenic linkage might facilitate reduction.

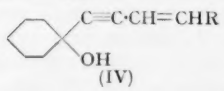
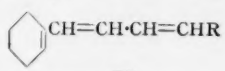
When the reaction was applied to diacetylenic glycols (I) the corresponding dienediols were formed. Material of *ca.* 87% purity was obtained only when 4 mols. of the hydride

$HO{\cdot}CR^1R^2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CR^1R^2{\cdot}OH$ (I) $\qquad$ $HO{\cdot}CR^1R^2{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CR^1R^2{\cdot}OH$ (II)

were used, and then with quite short reaction periods. It was also noted that the ultra-violet light-absorption curves of the products resulting from the action of smaller quantities of the reagent, and/or shorter reaction times, were consistent with the presence of (I) and (II) only; if the corresponding vinylacetylenic glycol had been present in appreciable quantity some deviation from additivity would have been expected. Under the optimal conditions a 40% yield of the pure diene glycol was obtained after further crystallisation.

By use of these optimal conditions, a number of other diacetylenic glycols (I) were reduced to the corresponding dienediols. Thus, where $R^1R^2 = [CH_2]_5$, $R^1 = R^2 = Ph$, and $R^1 = C_9H_{19}$, $R^2 = Me$, pure diene glycols were obtained in yields of 40%, 50%, and 25%, respectively. The simplest diacetylenic glycol (I; $R^1 = R^2 = H$) gave the expected diene in 26% yield. The glycol (I; $R^1 = H$, $R^2 = Me$) gave a liquid diene of about 88% purity (by ultra-violet spectroscopic assay); this compound has since been obtained pure as a low-melting solid by Ahmad, Sondheimer, Weedon, and Woods using our method. The glycol (I; $R^1 = H$, $R^2 = Ph$) (*J.*, 1952, 4089) gave a reduction product separable by chromatography into the expected diene-glycol and a hydrocarbon fraction. The former melted unsharply even after repeated crystallisation and was probably a mixture of *meso*- and racemic forms. The latter gave on repeated crystallisation all-*trans*-diphenylhexatriene; other hydrocarbons were probably present in the crude non-polar fraction.

Meanwhile, Chanley and Sobotka (*J. Amer. Chem. Soc.*, 1949, **71**, 4140) had described the reduction of 4-*cyclo*hex-1′-enylbut-3-yn-2-ol to the corresponding diene alcohol in good yield, only 0·63 mol. of lithium aluminium hydride being used. Such a method of reducing vinylacetylenic alcohols would be of great value, since inhomogeneous products are usually obtained by catalytic hydrogenation, while success in reductions with a zinc–copper couple (Nazarov and Fisher, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 1944, 341) apparently depends upon the quality of the zinc used, difficulty having been experienced with this reaction is these laboratories. Accordingly the alcohols (III) and (IV; R = H and Me)

$HO{\cdot}CMe_2{\cdot}C{\equiv}C{\cdot}CH{=}CH_2$ (III) $\qquad$  (IV) $\qquad$  (V)

were treated with lithium aluminium hydride under the conditions Chanley and Sobotka had used. In each case a good yield of the corresponding diene-alcohol was obtained; that from (IV; R = Me) was stable, but those derived from (III) and (IV; R = H), like hexa-3 : 5-dien-2-ol (Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84) and other 1-monosubstituted butadienes, were unstable and easily polymerised. These substances proved very susceptible to dehydration in presence of acids (whereas the vinylacetylenic alcohols are remarkably resistant—see Hamlet, Henbest, and Jones, *J.*, 1951, 2652), giving the unstable trienes (V; R = Me and H).

In view of these results with the vinylacetylenic alcohols $HO{\cdot}CR_2{\cdot}C{\equiv}C{\cdot}CH{=}CHR^1$, two alcohols $HO{\cdot}CR^1R^2{\cdot}CH{=}CH{\cdot}C{\equiv}CH$ ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = Me$) were investigated, a small excess (0·6 mol.) of the reagent being employed. That the products were the allenic alcohols, $HO{\cdot}CR^1R^2{\cdot}CH_2{\cdot}CH{=}C{=}CH_2$, was proved by ozonolysis, hydrogenation, the absence of intense ultra-violet light absorption, and by infra-red spectroscopy, a strong band at 1970 cm.$^{-1}$ indicating an allene grouping. The very convenient preparation of these alcohols should facilitate introduction of terminal allene systems into a wide variety of structures.

The reduction of the diacetylenic alcohol $HO{\cdot}CMe_2{\cdot}C{\equiv}C{\cdot}C{\equiv}CH$ gave the vinylacetylenic analogue $HO{\cdot}CMe_2{\cdot}CH{=}CH{\cdot}C{\equiv}CH$, previously prepared by anionotropic rearrangement (Jones and McCombie, *J.*, 1943, 261); similarly penta-2 : 4-diyn-1-ol gave pent-2-en-4-yn-1-ol. It is thus evident that the transformation:

$$HO{\cdot}CR_2{\cdot}C{\equiv}C{\cdot}C{\equiv}CH \longrightarrow HO{\cdot}CR_2{\cdot}CH{=}CH{\cdot}C{\equiv}CH \longrightarrow HO{\cdot}CR_2{\cdot}CH_2{\cdot}CH{=}C{=}CH_2$$

can be effected by two successive lithium aluminium hydride reductions, the same conditions being used in each. The product of the first reduction must be a complex incapable of further reaction since 4 mols. (possibly an unnecessary excess) of the reagent were employed in the reduction of the diacetylenic alcohol.

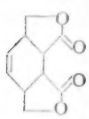
The method employed for the diacetylenic glycols was next applied to the higher polyacetylenic glycols recently described by Armitage, Cook, Jones, and Whiting (*J.*, 1952, 2010, 2014). When 5 mols. of the reagent were used, the glycols (VI; R = Me and Ph)

$$HO{\cdot}CR_2{\cdot}[C{\equiv}C]_3{\cdot}CR_2{\cdot}OH \qquad (VI)$$

$$HO{\cdot}CR_2{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CR_2{\cdot}OH \qquad (VII)$$

gave the corresponding divinyl acetylenic glycols (VII) in *ca.* 50% yield—a good example of the specificity of this reaction. The tetra-acetylenic glycol $HO{\cdot}CMe_2{\cdot}[C{\equiv}C]_4{\cdot}CMe_2{\cdot}OH$, similarly gave $HO{\cdot}CMe_2{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CMe_2{\cdot}OH$, easily recognised by the very characteristic ultra-violet absorption properties of its unsaturated system.

Stereochemistry of the Reduction Products.—In the catalytic hydrogenation of acetylenic compounds *cis*-ethylenes are usually obtained, but chemical reduction usually gives products of *trans*-configuration (see Greenlee and Fernelius, *J. Amer. Chem. Soc.*, 1942, **64**, 2505; Crombie, *Quart. Reviews*, 1952, **6**, 101). In the present work *trans*-ethylenes were apparently formed in every case. The glycol obtained from $HO{\cdot}CPh_2{\cdot}[C{\equiv}C]_2{\cdot}CPh_2{\cdot}OH$ differs from the previously-described material resulting from catalytic hydrogenation, and more direct evidence is provided by the occurrence of strong absorption in the infra-red near 960 cm.$^{-1}$ in six reaction products containing diene, vinylacetylene, and vinylethynylvinyl groupings. In no case was a strong band observed in the 680—730-cm.$^{-1}$ region typical of simple *cis*-ethylenes. The ultra-violet absorption spectra of the glycols (II) confirm this conclusion. Braude and Coles (*J.*, 1951, 2085) showed that allylic hydroxyl groups increased the intensity of absorption of *trans*- but not of *cis*-1-substituted butadienes; and the even greater absorption intensity of these glycols, relative to hexa-2 : 4-diene, implies that both ethylenic linkages are probably *trans*. Final proof of the *trans-trans*-configuration of the glycol (II; R = H) was obtained by means of a Diels–Alder reaction with maleic anhydride, which gave the dilactone (VIII). This reaction was complicated by the simultaneous occurrence of polymer formation, and gave a yield of only 20%; however, Diels–Alder reactions even with *cis*-piperylene are known to proceed with such difficulty (see *inter al.*, Craig, *J. Amer. Chem. Soc.*, 1950, **72**, 1678) that this reaction can be considered good evidence of a *trans-trans*-configuration.



(VIII)

In earlier attempts to obtain chemical confirmation of the double-bond configuration in the glycols (II), the three isomeric methyl muconates were prepared by the method of Elvidge, Linstead, Orkin, Sims, Baer, and Pattison (*J.*, 1950, 2228, 2235). All, however, gave little or none of the expected primary glycols on treatment with lithium aluminium hydride under varied conditions, and the *trans-trans*-ester also failed to react normally with methylmagnesium iodide.

The ultra-violet absorption spectra of certain of the compounds obtained have been discussed above inasmuch as they assist in identification; but in the case of the diene alcohols and glycols, constitution and purity may be assured independently, and some interesting correlations may be deduced. The results are tabulated.

The data for a range of diene glycols (II) add to the evidence in favour of small but definite hyperchromic and bathochromic effects resulting from the introduction of a hydroxyl group on a carbon atom adjacent to a diene system, as was first observed by Braude and Coles (*loc. cit.*). However, it appears that a marked increase in the intensity of absorption of a 1 : 4-disubstituted diene also results when the length of the existing

alkyl group is considerably increased—indeed it has been suggested, in view of the higher ε values obtained with long-chain dienes that the value for $\varepsilon_{max.}$ quoted for hexa-2 : 4-diene is too low (Bolland and Koch, *J.*, 1945, 445), although considerable care was taken by Gillam *et al.* (*loc. cit.*) to avoid errors due to the polymerisation of the simple hydrocarbon.

TABLE 1. *Light absorption of* trans-trans-*dienes*, CHR=CH·CH=CHR.

R	R¹	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	Ref.	R	R¹	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$
Me ...	Me	2270	22·5	[1]	CH_2·OH	CH_2·OH	2290	31
C_6H_{13}	$[CH_2]_7$·CO_2H	2310	29	[2]	CMe_2·OH	CMe_2·OH	2290	32
Me ...	C<$[CH_2]_5$·OH	2305	27·5		CMe(C_9H_{19})·OH	CMe(C_9H_{19})·OH	2305	39
					C<$[CH_2]_5$·OH	C<$[CH_2]_5$·OH	2330	33

TABLE 2. *Light absorption of* trans-*dienes*, CHR=CH·CH=CH_2.

R	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$	Ref.	R	$\lambda_{max.}$ (Å)	$10^{-3}\varepsilon$
Me	2230	23·0	[1]	CMe_2·OH	2240	24·5 *
CHMe·OH	2230	28·0	[3]	C<$[CH_2]_5$·OH	2260	22 *

* Intensity values may be low.

[1] Booker, Evans, and Gillam, *J.*, 1940, 1453; configuration probable from method of formation. [2] Nichols, Herb, and Riemenschneider, *J. Amer. Chem. Soc.*, 1951, **73**, 247. [3] Heilbron, Jones, McCombie, and Weedon, *loc. cit.*

If the effect is real, the remarkably high intensity observed (and verified by replicate determinations) for (II; R^1 = Me, $R^2 = C_9H_{19}$) is at once explicable, as both of these hyperchromic effects would be simultaneously operative. Much scattered evidence supports the postulated weight effect (cf. Koch, *J.*, 1948, 1123, for an example involving the β-alkylstyrene chromophore); it evidently involves also a small bathochromic shift (*ca.* +10 Å for each substitution of C_6H_{13} for Me).

Another, and quite distinct, small effect discernible in the figures quoted is the bathochromic effect resulting from the substitution of 1-hydroxy*cyclo*hexyl for 1-hydroxy-1-methylethyl or hydroxymethyl. This implies that the effect of an exocyclic environment observed by Woodward (*J. Amer. Chem. Soc.*, 1942, **64**, 72) as responsible for a shift of +50 Å in the absorption maximum of a conjugated diene, is paralleled by a similar but smaller shift (+20 Å) when the exocyclic bond is that joining a ⩾C–OH group to the diene system. The double operation of this effect brings $\lambda_{max.}$ for (II; $R^1R^2 = [CH_2]_5$) to 2330 Å, perhaps the first instance of a simple disubstituted diene found to absorb maximally at or above the wave-length given by Woodward (*loc. cit.*) for trisubstituted dienes (2320 Å).

The glycols (II; $R^1 = R^2$ = Ph) and (II; R^1 = Ph, R = H) showed maxima displaced by +120 Å and +135 Å, respectively, and intensified when compared with the aliphatic glycols. Similar displacements were observed in the cases of (X; R = Ph), where the system ·CH=CH·C≡C·CH=CH· is involved, and the diacetylenic glycols (I; $R^1 = R^2$ = Ph) and (I; R^1 = Ph, R^2 = H) discussed earlier (Armitage, Cook, Entwistle, Jones, and Whiting, *J.*, 1952, 1998). Evidently interaction through >CR·OH groupings between aryl or alkenyl groups and unsaturated systems of varied types is a general phenomenon.

EXPERIMENTAL

"Lithium aluminium hydride" refers to a commercial grade estimated to contain about 85% of the actual reagent, melting-points were determined on the Kofler block, and ultraviolet absorption spectra were determined in absolute ethanol with a Unicam SP 500 spectrophotometer.

Reduction of Methyl Phenylpropiolate.—(*a*) A solution of lithium aluminium hydride (0·5M; 62·5 c.c.) in ether was cooled to −78° while methyl phenylpropiolate (10·0 g.) was added dropwise. After 5 min., water (5 c.c.) was added, and the mixture was allowed to reach room temperature. Isolation of the product and distillation of the neutral fraction gave fairly pure phenylpropargyl alcohol (7·9 g., 96%), b. p. 103—105°/1·5 mm., n_D^{18} 1·5820, $\lambda_{max.}$ 2420 and 2510 Å (ε = 14,600 and 13,600, respectively). Its 3 : 5-*dinitrobenzoate* had m. p. 131—132°. An authentic specimen, n_D^{24} 1·5834, $\lambda_{max.}$ 2410 and 2500 Å (ε = 16,900 and 14,000, respectively) (Lai, *Bull. Soc. chim.*, 1933, **53**, 682), gave an identical 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 131—132° (Found : N, 8·4. $C_{16}H_{10}O_6N_2$ requires N, 8·6%).

(*b*) When, in the above experiment, 94 c.c. of the standard solution of the hydride and a reaction-time of 15 min. at room temperature were employed, the distillate (6·9 g., 83%) had b. p. 78°/0·5 mm., n_D^{15} 1·5852, $\lambda_{max.}$ 2500, $\lambda_{infl.}$ 2485 Å (ε = 17,400 and 17,200, respectively). Recrystallisation of the partly solidified product from light petroleum gave *trans*-cinnamyl alcohol (2·0 g.), m. p. 33° undepressed on admixture with an authentic specimen, which had $\lambda_{max.}$ 2510, $\lambda_{infl.}$ 2485 Å, ε = 19,600 and 19,400, respectively.

1-*Vinyl*cyclo*hexanol*.—A mixture of 1-ethynyl*cyclo*hexanol (4·0 g.) and lithium aluminium hydride (2·0 g.) in dioxan (100 c.c.) was refluxed for 1 hr. Addition of water and distillation of the product gave 1-vinyl*cyclo*hexanol (3·0 g.), b. p. 62—64°/11 mm., n_D^{14} 1·4758 (Nazarov *et al.*, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1946, 305, give b. p. 67·5—68°/15 mm., n_D^{20} 1·4740). No precipitate was obtained with ammoniacal silver nitrate solution. The 3 : 5-dinitrobenzoate melted at 103·5—104° (Cook and Lawrence, *J.*, 1938, 61, give m. p. 101—102°).

1-*Ethyl*cyclo*hexanol*.—A mixture of 1-ethynyl*cyclo*hexanol (6·2 g.) and lithium aluminium hydride (5·0 g.) in dioxan (250 c.c.) was heated under reflux for 18 hr. Isolation of the product as above gave 1-ethyl*cyclo*hexanol (4·5 g., 71%), b. p. 67°/16 mm., n_D^{18} 1·4678 (Williams and Edwards, *J. Amer. Chem. Soc.*, 1947, **69**, 336, give b. p. 77°/20 mm., n_D^{25} 1·4618). No hydrogen was absorbed over reduced platinic oxide; the 3 : 5 dinitrobenzoate had m. p. 127·5—128·5° (Cook and Lawrence, *loc. cit.*, give m. p. 127—127·5°).

1-*Phenylprop*-2-*en*-1-*ol*.—1-Phenylprop-2-yn-1-ol (5·0 g.) was added to an ethereal suspension of lithium aluminium hydride (3·6 g.), and the mixture was heated under reflux for 4 hr. Decomposition of the complex and distillation of the neutral fraction yielded the alcohol (4·75 g., 94%), b. p. 56°/0·05 mm., n_D^{16} 1·5410 (Braude, Jones, and Stern, *J.*, 1946, 396, give b. p. 53—54°/0·15 mm., $n_D^{14\cdot5}$ 1·5464). The *p*-nitrobenzoate formed plates, m. p. 45·5—46°, from methanol (Burton and Ingold, *J.*, 1928, 904, give m. p. 45—46°).

2-*Methylhexa*-3 : 5-*dien*-2-*ol*.—To a stirred suspension of lithium aluminium hydride (1·08 g.) in ether (300 c.c.), 2-methylhex-5-en-3-yn-2-ol (Nazarov and Torgov, *Zhur. Obshchey Khim. S.S.S.R.*, 1948, **18**, 1332) was added, and the mixture was heated under reflux for 3 hr. Distillation of the product gave the diene-alcohol (4·48 g., 88%), b. p. 55°/12·5 mm., $n_D^{20\cdot5}$ 1·4758 (Found: C, 74·6; H, 10·35. Calc. for $C_7H_{12}O$: C, 74·9; H, 10·7%). Nazarov and Fisher, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 1942, 135, record b. p. 42—43°/9 mm., n_D^{20} 1·4693.

1-1′-*Hydroxy*cyclo*hexylbuta*-1 : 3-*diene*.—Reduction of 1-1′-hydroxy*cyclo*hexylbut-3-en-1-yne (2·0 g.) (Hamlet, Henbest, and Jones, *loc. cit.*) with lithium aluminium hydride (0·32 g.) for 3 hr. at 35° gave, after distillation, the *diene-alcohol* (1·38 g.), b. p. 100°/13 mm., n_D^{24} 1·5075, m. p. 23° (Found: C, 79·1; H, 10·75. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%).

1-1′-*Hydroxy*cyclo*hexylpenta*-1 : 3-*diene*.—Similar reduction of the higher homologue (*ibid.*, *loc. cit.*; mixture of *cis*- and *trans*-isomers) (5·0 g.) gave the corresponding *diene* (3·95 g.), b. p. 87°/0·7 mm., $n_D^{19\cdot5}$ 1·5192 (Found: C, 79·2; H, 10·9. $C_{11}H_{18}O$ requires C, 79·4; H, 10·9%).

1-cyclo*Hex*-1′-*enylbuta*-1 : 3-*diene*.—This was prepared by distilling the corresponding tertiary alcohol from a little potassium hydrogen sulphate. The product, dissolved in light petroleum, was passed through alumina. The very unstable *hydrocarbon* had b. p. 145° (bath temp.)/14 mm., n_D^{21} 1·5594, $\lambda_{max.}$ 2555, 2650, and 2750 Å (ε = 32,300, 43,400, and 34,500, respectively) (Found: C, 89·3; H, 10·65. $C_{10}H_{14}$ requires C, 89·5; H, 10·5%).

1-cyclo*Hex*-1′-*enylpenta*-1 : 3-*diene*.—Prepared similarly, this had b. p. 70° (bath temp.)/0·1 mm., n_D^{20} 1·5605, $\lambda_{infl.}$ 2600, $\lambda_{max.}$ 2670 and 2770 Å (ε = 27,500, 36,800, and 29,100, respectively) (Found: C, 88·75; H, 10·95. $C_{11}H_{16}$ requires C, 89·1; H, 10·9%).

Penta-3 : 4-*dien*-1-*ol*.—Reduction of pent-2-en-4-yn-1-ol (6·0 g.; Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583) with lithium aluminium hydride (1·7 g.) at 35° for 3 hr. gave the allenic *alcohol* (5·1 g.), b. p. 57—58°/16 mm., n_D^{23} 1·4760 (Found: C, 69·1, 69·9; H, 8·7, 9·1. C_5H_8O requires C, 71·4; H, 9·6%). Catalytic hydrogenation over reduced platinic oxide resulted in an uptake of 2·2 mol. A 3 : 5-*dinitrobenzoate*, m. p. 39—40·5°, was obtained (Found: C, 51·9; H, 3·7; N, 10·0. $C_{12}H_{10}O_6N_2$ requires C, 51·8; H, 3·65; N, 9·9%).

Hexa-4 : 5-*dien*-2-*ol*.—Reduction of hex-3-en-5-yn-2-ol (8·0 g.; Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54) with lithium aluminium hydride (2·05 g.) as above gave the allenic *alcohol* (5·4 g.), b. p. 54—55°/14 mm., n_D^{18} 1·4718 (Found: C, 73·1; H, 10·5. $C_6H_{10}O$ requires C, 73·4; H, 10·25%). Hydrogenation over reduced platinic oxide (absorption 2·05 mol.) and oxidation with chromic acid gave hexan-2-one, isolated as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 108—109°. On ozonolysis in acetic acid solution, formaldehyde was obtained, isolated in 59% yield as the dimedone derivative, m. p. and mixed m. p. 188—189°.

Pent-2-*en*-4-*yn*-1-*ol*.—Penta-2 : 4-diyn-1-ol (3·0 g.; Armitage, Jones, and Whiting, *J.*, 1952,

1993) was added to an ethereal suspension of lithium aluminium hydride (2·85 g.), and the mixture was heated under reflux for 4 hr. Isolation of the product gave pent-2-en-4-yn-1-ol (1·7 g.), b. p. 61°/10 mm., n_D^{20} 1·4970 (Haynes *et al.*, *loc. cit.*, give b. p. 71—73°/19 mm., n_D^{19} 1·4972).

2-Methylhex-3-en-5-yn-2-ol.—Treatment of 2-methylhexa-3 : 5-diyn-2-ol (4·9 g.; Armitage, Jones, and Whiting, *loc. cit.*) with lithium aluminium hydride (7·7 g.) as above gave the vinylacetylenic alcohol (3·45 g.), b. p. 69—73°/22 mm., $n_D^{15\cdot5}$ 1·4764 (Jones and McCombie, *loc. cit.*, give b. p. 91—93°/50 mm., $n_D^{24\cdot5}$ 1·4711). Light absorption: maximum, 2230 Å, inflexion, 2310 Å; ε = 12,200 and 9100, respectively.

Diacetylenic Glycols.—In preliminary experiments with (I; $R^1 = R^2$ = Me) reaction time and reagent proportions were varied independently, the total glycol fraction (insoluble in cold benzene) being analysed spectroscopically. All products gave the diene-glycol (II) on repeated crystallisation, in low yield when smaller quantities of the hydride were employed. The use of more than 4 mol. of reagent did not increase the purity of crude (II), but did reduce the total glycol fraction.

General Method for Diacetylenic Glycols.—To a stirred mixture of lithium aluminium hydride (4·5 mol.) and ether (100 c.c./g.) the diacetylenic glycol (Armitage, Jones, and Whiting, *J.*, 1951, 44) was added, and the mixture was heated under reflux for 4—18 hr.; the reaction period was not critical. Addition of ethyl acetate, then sulphuric acid, and isolation of the neutral fraction gave a syrup which was dissolved in warm benzene. The solid which separated on cooling was recrystallised to constant melting point and ultra-violet absorption intensity. The following were thus obtained:

trans-trans-*2 : 7-Dimethylocta-3 : 5-dien-2 : 7-diol* (2·0 g.) [from the corresponding diacetylenic glycol (5·0 g.)] as needles, m. p. 107—108° (from benzene) (Found: C, 70·3; H, 10·6. $C_{10}H_{18}O_2$ requires C, 70·55; H, 10·7%). Unlike the starting material, the diene-glycol decomposed partly in a few weeks in air at room temperature.

10 : 15-Dimethyltetracosa-11 : 13-diene-10 : 15-diol, m. p. 104—105°, in 25% yield (Found: C, 79·05; H, 12·55. $C_{26}H_{50}O_2$ requires C, 79·1; H, 12·75%).

*1 : 4-Bis-1′-hydroxy*cyclo*hexylbuta-1 : 3-diene*, obtained in 40% yield, had m. p. 115—116° after crystallisation from light petroleum (b. p. 60—80°) (Found: C, 76·5; H, 10·5. $C_{16}H_{26}O_2$ requires C, 76·75; H, 10·5%).

1 : 1 : 6 : 6-Tetraphenylhexa-2 : 4-diene-1 : 6-diol, m. p. 177°, was obtained in 50% yield (Found: C, 86·35; H, 6·25. $C_{30}H_{26}O_2$ requires C, 86·1; H, 6·25%).

Hexa-2 : 4-diene-1 : 6-diol.—The corresponding diacetylenic glycol (8·0 g.) was reduced with lithium aluminium hydride (13·8 g.; crude), and the product was isolated by continuous extraction with ether. Sublimation of the resultant semi-solid material at 10^{-4} mm. followed by four recrystallisations from benzene gave the diene-glycol (2·2 g., 27%), m. p. 105·5—106·5° (Found: C, 63·35; H, 6·65. Calc. for $C_6H_{10}O_2$: C, 63·15; H, 6·85%) (Prévost, *Ann. Chim.*, 1928, **10**, 398, gives m. p. 105°).

*3 : 6-Bishydroxymethyl*cyclo*hex-4-ene-1 : 2-dicarboxylic Dilactone.*—The above glycol (350 mg.), maleic anhydride (300 mg.), and benzene (40 c.c.) were heated under reflux for 30 min., set aside at 20° for 18 hr., and then evaporated to dryness. Crystallisation of the product from ethanol gave the *dilactone* (120 mg., 20%) as needles, m. p. 167·5—168·5° (Found: C, 62·0; H, 5·25. $C_{10}H_8O_4$ requires C, 61·85; H, 5·2%).

1 : 6-Diphenylhexa-1 : 3 : 5-triene and trans-trans-*1 : 6-Diphenylhexa-2 : 4-diene-1 : 6-diol.*—Reduction of 1 : 6-diphenylhexa-2 : 4-diyne-1 : 6-diol (6·6 g.) by the general method for 4 hr. gave a neutral fraction which was separated into (*a*) a portion soluble in cold benzene (3·9 g.), and (*b*) an insoluble residue. The former was passed through alumina (deactivated) in benzene solution, then crystallised three times from light petroleum, giving diphenylhexatriene (1·7 g., 30%), m. p. 197—200° (Found: C, 93·1; H, 6·8. Calc. for $C_{18}H_{16}$: C, 93·1; H, 6·9%). Light absorption: maximum, 3525 Å, inflexions, 3360 and 3685 Å (ε = 66,000, 53,500, and 49,000, respectively). Kuhn *et al.* (*Z. physikal. Chem.*, 1935, **29**, *B*, 384) give m. p. 200° and ultra-violet maxima at 3350, 3490, and 3700 Å (ε = 54,000, 67,000, and 55,000, respectively).

The residue (*a*) was recrystallised from hot benzene to give the trans-trans-*glycol* (1·8 g., 27%), m. p. 108·5—111° not altered on recrystallisation (Found: C, 80·85; H, 6·95. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%). Kuhn *et al.* (*Ber.*, 1938, **71**, 1889) give m. p. 103—104° for the glycol (*cis-cis* ?) obtained by catalytic semihydrogenation.

2 : 9-Dimethyldeca-3 : 7-dien-5-yne-2 : 9-diol.—Reduction, by the general method used for diacetylenic glycols, of 2 : 9-dimethyldeca-3 : 5 : 7-triyne-2 : 9-diol (2·0 g.; Armitage, Cook, Jones, and Whiting, *J.*, 1952, 2010) gave the divinylacetylenic *glycol* (0·9 g., 44%), which

formed needles, m. p. 120·5—121·5, after recrystallisation from benzene (Found: C, 74·1; H, 9·15. $C_{12}H_{18}O_2$ requires C, 74·15; H, 9·35%). Light absorption: maxima, 2635 and 2780 Å (ε = 22,800 and 18,400); inflexion, 2150 Å (ε = 9200) (cf. Heilbron, Jones, *et al.*, *J.*, 1945, 77).

1 : 1 : 8 : 8-*Tetraphenylocta*-2 : 6-*dien*-4-*yne*-1 : 8-*diol*.—The triacetylenic glycol from benzophenone (3·0 g.) was reduced as described above, giving after 4 hr. the *tetraphenyloctadienynediol* (1·75 g., 58%) as irregular plates, m. p. 161—162°, from benzene (Found: C, 86·5; H, 6·05. $C_{32}H_{26}O_2$ requires C, 86·8; H, 5·9%). Light absorption: maxima, 2755 and 2860 Å (ε = 28,400 and 22,700, respectively).

2 : 11-*Dimethyldodeca*-3 : 9-*diene*-5 : 7-*diyne*-2 : 11-*diol*.—Reduction of the corresponding tetrayne-glycol (Armitage, Jones, and Whiting, *J.*, 1952, 2014) at the boiling-point gave a crude product the ultra-violet absorption spectrum of which suggested over-reduction. When, however, the glycol was stirred with 5 mols. of the hydride at room temperature for 18 hr., the characteristic bands of the expected chromophore were prominent in the crude neutral product. This, a red syrup (2·0 g. from 2·0 g. of the starting material) was dissolved in warm benzene (10 c.c.) and treated with animal charcoal. When the solution cooled, crystals (0·4 g.; m. p. 92—105°) separated, and were purified by chromatography on deactivated alumina. Recrystallisation of the product (0·3 g.; m. p. 104—114°) from aqueous methanol gave needles, m. p. 123—125° (Found: C, 77·1; H, 8·45. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). Light absorption: maxima, 2290, 2360, 2480, 2620, 2760, 2930, and 3120 Å (ε = 33,100, 33,700, 25,700, 9400, 17,600, 27,300, and 22,300, respectively) (cf. Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579).

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Researches on Acetylenic Compounds. Part XLIII. A New Method for the Preparation of Alkoxyacetylenes.*

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A new and very convenient method for the preparation of the alkoxyacetylenes is described. Some of their properties, including their ability to convert acids into their anhydrides under very mild conditions, are summarised.

IN Part XXXVIII (Eglinton, Jones, and Whiting, *J.*, 1952, 2873) a reaction was described which involved the elimination of HX and ROH from αβ-halogeno-ethers in the presence of sodamide:

$$R'CH(OR)\cdot CHXR'' \xrightarrow{NaNH_2} R'C{\equiv}CR''$$

This method has now been extended to the preparation of alkoxyacetylenes (R′ = OAlk, R″ = H). These are valuable synthetic agents, giving αβ-unsaturated esters by condensation with carbonyl compounds and treatment with acids, or αβ-unsaturated aldehydes when an intermediate hydrogenation stage is employed; yields are good (see Arens and van Dorp, *Nature*, 1947, **160**, 189; Clemo and Davison, *J.*, 1951, 447; Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823; Sarett, Arth, Lukes, Beyler, Poos, Johns, and Constantin, *J. Amer. Chem. Soc.*, 1952, **74**, 4974) but these methods have been little used because of the inaccessibility of alkoxyacetylenes by present methods (Jacobs, Kramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 1223; van Dorp, Arens, and Stephenson, *Rec. Trav. chim.*, 1951, **70**, 289; Favorskii and Shchukina, *Chem. Abs.*, 1944, **38**, 300).

* Part XLII, preceding paper.

Dimethyl chloroacetal was used for preliminary quantitative experiments, which showed that the reaction followed the expected course :

$$Cl{\cdot}CH_2{\cdot}CH(OMe)_2 + 3NH_2^- \longrightarrow \bar{C}{\equiv}C{\cdot}OMe + \bar{C}l + \bar{O}Me + 3NH_3$$

since after 15 minutes 1, 2, and 3 mols. of sodamide had liberated 0·31, 0·61, and 0·91 mols. of ionic chlorine, respectively. After an hour the figures were substantially the same. Isolation of the very volatile product proved difficult, since if liberated from its sodium derivative by ammonium chloride it was lost on evaporation of the ammonia. On the other hand isolation of the sodium compound without acidification resulted in a series of explosions, due to its extraordinary sensitivity to air. Even when air was excluded, the dry solid underwent decomposition above about 60°. Eventually the technique described below was developed; a variant has been found satisfactory by Professor A. C. Cope and his collaborators (*Org. Synth.*, in the press). It is recommended that one of these procedures be followed exactly, since otherwise this method is hazardous. It is, however, overwhelmingly more convenient than the older routes to alkoxyacetylenes, giving in a single operation a 60% yield and being practicable on quite a large scale.

With obvious modifications this method was readily applied to the preparation of ethoxy- and butoxy-acetylenes, the requisite dibutyl chloroacetal being obtained from the methyl compound by an alcohol-interchange reaction. The bromoacetals could be substituted for the chlorine compounds, but without advantage. Attempts to convert α-bromopropionaldehyde dimethylacetal into 1-methoxyprop-1-yne, however, were unsuccessful; the main constituent of the heterogeneous product was the acetal of acraldehyde.

Some clarification of the mechanism of the acetylene-synthesis from β-halogeno-ethers described by Eglinton, Jones, and Whiting (*loc. cit.*), and further exemplified above, is now possible as a result of the work of Hill, Judge, Skell, Kantor, and Hauser (*J. Amer. Chem. Soc.*, 1952, **74**, 5599). These authors proved that when 1-octyl bromide was treated with potassamide in liquid ammonia, about 10% of the oct-1-ene (the major product) was formed by removal of one of the hydrogen atoms of the bromomethyl grouping, with hydrogen shift from the neighbouring methylene group, *i.e.*,

$$C_6H_{13}{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{H_2N^-} [C_6H_{13}{\cdot}CH_2{\cdot}CH<] \longrightarrow C_6H_{13}{\cdot}CH{=}CH_2$$

Presumably, proximity to the C–Br dipole activates a proton sufficiently for removal by H_2N^-, the synchronous separation of Br^- from the incipient carbanion lending some assistance even though an energy-rich diradical remains. Possibly (though the distortions from normal molecular dimensions are then numerous) the hydrogen-shift is concerted with the initial attack. Now, if the bromomethyl or chloromethyl group were adjacent to a carbon atom bearing an ether linkage, the main factor, proximity to the C–halogen linkage, would still operate; but RO^- might be lost simultaneously from the β-carbon atom, instead of halide ion from the α-atom. In compensation for the smaller energy gain in the ion-formation process a more stable main product, an ethylenic compound instead of a diradical, would result; or alternatively, the further complexity in the transition state implied by a simultaneous hydrogen migration would be avoided. Eglinton, Jones, and Whiting (*loc. cit.*) had assumed tacitly that when a compound R′CHX·CHR″·OR was treated with sodamide, the only possible initial single-elimination process would give the vinyl ether R′CH:CR″·OR, since dehydrohalogenations are easy, and dehydroalkoxylations are much more difficult to effect. Now that the work of Hill *et al.* (*loc. cit.*) has directed attention to the role of the α-substituent, a two-stage mechanism for the observed overall reaction, *i.e.*, $R'CHX{\cdot}CHR''{\cdot}OR \longrightarrow RO^- + R'{\cdot}CX{=}CHR'' \longrightarrow R'C{\equiv}CR'' + X^-$ becomes plausible and indeed preferable to the double-elimination hypothesis advanced earlier. It is supported by the contrasting effects of sodamide on the acetals of α-bromopropaldehyde and bromoacetaldehyde (see above). Secondary carbanions are less stable (and hence less easily formed, and more reactive) than primary carbanions (see *inter al.*, Gilman, Moore, and Bame, *J. Amer. Chem. Soc.*, 1941, **63**, 2479), a fact which would account for the failure of the former acetal to give 1-methoxyprop-1-yne. Competition from proton-

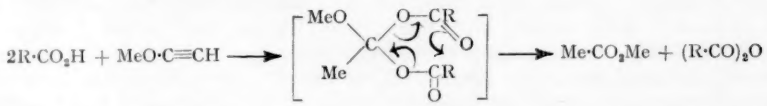
elimination at the methyl group is not alone an adequate explanation of this result, since the propionacetal reacted much more slowly than its lower homologue, as proved by the absence, in this case, of obvious liberation of heat, and by a determination of the amount of bromide ion liberated after 30 minutes (only 0·77 mol.).

The condensation of sodiomethoxy- or sodioethoxy-acetylene with carbonyl compounds *in situ* offers an apparently attractive route to αβ-ethylenic esters, etc. This was investigated with acetone, benzaldehyde, and *cyclo*hexanone. β-Methylcrotonic acid was indeed obtained in the first place, but despite wide variations in reaction conditions, the substitution of lithium or potassium for sodium, or the preparation of sodioethoxyacetylene from pre-formed ethoxyacetylene, yields remained very low.

For alkylation *in situ*, effectively an alternative to the use of malonic ester alkylation in the synthesis of fatty acids, the presence of sodium alkoxide might well be disadvantageous. A second new route to alkoxyacetylenes from vinyl ethers was therefore sought. This involved merely the usual bromination–dehydrobromination sequence, the second reaction being effected in one operation by using sodamide (3 mols.) in liquid ammonia. Precautions were necessary to avoid the rapid reaction of the αβ-dibromo-ethers with ammonia vapour; commercially available 1 : 2-dichloroethyl ethyl ether could also be used. In this way butyl bromide was converted into hexanoic acid in 17% overall yield, which could probably be improved considerably.

Some properties of the alkoxyacetylenes are summarised in the Experimental section; we would emphasise that, once prepared, they are stable for weeks at 0° and quite safe to handle.

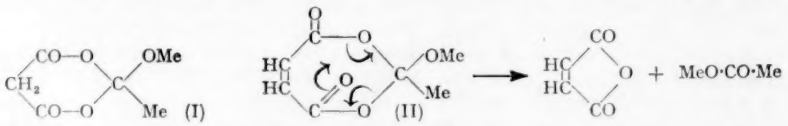
Methoxyacetylene reacted exothermically with acetic and butyric acids, giving methyl acetate and the corresponding anhydrides:



Presumably an unstable di-adduct decomposes through a cyclic transition state, in a reaction analogous to the decomposition of ethylidene diacetate into acetaldehyde and acetic anhydride (G.P. 284,996; *Chem. Zent.*, 1915, II, 294), the reaction taking place even at 0°. As no mono-adduct was obtained from an equimolecular mixture, it must be assumed that the mono-adduct is more reactive toward the acid than methoxyacetylene, as are the structurally similar keten acetals.

This method seemed to be the mildest yet devised for converting a carboxylic acid into its anhydride; heptanoic, phenylacetic, β-phenylpropionic, acrylic, chloroacetic, and trichloroacetic acids all gave their anhydrides at or below room temperature. Others were less reactive, and the use of phosphoric acid and mercuric oxide as catalysts (cf. Reppe, G.P. 588,352; 589,970) was investigated. A marked increase in reaction rate was observed in comparative experiments, crotonic and pivalic acids now reacting smoothly at room temperature. Cinnamic and palmitic acids, however, were still inert, possibly because of their insolubility.

Other acids presented points of especial interest. Formic acid reacted vigorously, even at 0°, without a catalyst, but carbon monoxide was the only product—a result which



sets a lower limit to the possible stability of formic anhydride. Oxalic acid reacted similarly, though more slowly, evolving carbon monoxide and carbon dioxide. Malonic acid reacted vigorously and gave a syrupy product from which a small quantity of liquid, b. p. 85—95°/1 mm., could be separated by heating to 240°/1 mm. This appeared to be essen-

tially (I), a small proportion of enol being present, though analytical data were only approximately correct for $C_6H_8O_5$. It may perhaps have been formed by thermal depolymerisation; its properties closely resemble those of *iso*propylidene malonate (Davison and Bernhard, *J. Amer. Chem. Soc.*, 1948, **70**, 3426). Maleic acid gave an excellent yield of the anhydride; in this case the rearrangement of the initially-formed cyclic ester (II) can take place much more easily than with (I).

By this reaction the anhydride was obtained in good yield from toluene-*p*-sulphonic acid.

Work on this reaction was stopped when it was learnt that Arens and Moddermann (see *Chem. Abs.*, 1951, **45**, 6152) had discovered it independently, and in general obtained very similar results.

Experimental

Ethoxyacetylene.—A suspension of sodamide in liquid ammonia was prepared from sodium (38 g.) and liquid ammonia (500 ml.) in a 1-l. round-bottomed flask, clamped to the bottom of a vertical Duralumin rod (length 30″), the top of which was fixed. By using this system, the contents of the flask could be swirled very conveniently. Diethyl chloroacetal (76·5 g.; commercial) was added during 15—20 min. with manual agitation. The ammonia was evaporated in a stream of pure nitrogen. The flask was then cooled to −70° (nitrogen flow maintained), and a cold (−20°) saturated solution of sodium chloride (325 ml.) was added as rapidly as possible, with vigorous agitation. The flask was then fitted with a still-head connected to a trap cooled to −30°, and the contents of the flask were slowly heated to 100°. The condensate was allowed to warm to 0° and neutralised by the addition of an aqueous slurry of sodium dihydrogen phosphate. The aqueous layer was frozen and the supernatant liquid was decanted and dried ($CaCl_2$). Distillation (15-cm. Fenske column) gave ethoxyacetylene (21·2 g., 61%), b. p. 50—52°, n_D^{20} 1·3796 (Favorskii and Shchukina, *loc. cit.*, give b. p. 50°, n_D^{20} 1·3796; Jacobs, Cramer, and Hanson, *loc. cit.*, give n_D^{20} 1·3812).

Methoxyacetylene.—This was prepared as above from sodium (36 g.), liquid ammonia (500 ml.), and dimethyl chloroacetal (62 g.; commercial). Distillation gave methoxyacetylene (16·0 g., 57%), b. p. 22·5—23·5°/760 mm., n_D^{18} 1·3677, d_D^{18} 0·805 (Favorskii and Shostakovskii, *loc. cit.*, give b. p. 22—26°).

Dibutyl Chloroacetal.—A mixture of dimethyl chloroacetal (77·5 g.), *n*-butanol (92·5 g.), and sulphuric acid (0·1 ml.) was heated; when the theoretical quantity of methanol (50 ml.) had been collected the residue was cooled, neutralised with potassium carbonate, and distilled to give dibutyl chloroacetal (109·2 g., 84%), b. p. 71°/0·4 mm., n_D^{18} 1·4311 (Shostakovskii and Sidel'kovskaya, *Zhur. Obshchey Khim. S.S.S.R.*, 1950, **20**, 620, give b. p. 113—114°/13 mm., n_D^{20} 1·4310).

Butoxyacetylene.—Dibutyl chloroacetal (104·3 g.) was added during 1½ hr. to a suspension of sodamide [from sodium (38 g.)] in liquid ammonia (500 ml.). After a further 2½ hr. (during which more liquid ammonia was added to replace losses), a cold (−15°) concentrated ammonia solution (*d* 0·88; 150 ml.) was added, followed by water (200 ml.). The organic layer was separated, filtered, and distilled. After being washed with water and dried (anhydrous calcium chloride), the product was redistilled (15-cm. Fenske column), giving butoxyacetylene (21·7 g., 44%), b. p. 41—42/78 mm., $n_D^{16.5}$ 1·4067, $n_D^{4.5}$ 1·4128 (Jacobs, Cramer, and Hanson, *loc. cit.*, give b. p. 50·5°/110 mm.; Shchukina and Favorskii, *loc. cit.*, give n_D^{20} 1·4010).

n-*Hexanoic Acid.*—1 : 2-Dichloroethyl ethyl ether (13·7 g.) was added to a stirred suspension of sodamide [from sodium (7·0 g.)] in liquid ammonia (300 ml.). The resultant suspension of sodium ethoxyacetylide was treated with *n*-butyl bromide (13·3 g.) and stirred for 2 hr. After the ammonia had evaporated, water was added and the product was isolated with ether. Evaporation of the solvent gave crude 1-ethoxyhex-1-yne (5·2 g.) which could not be distilled owing to persistent foaming; it was therefore added portionwise to a mixture of ethanol (10 ml.), water (10 ml.), sulphuric acid (2N; 2 ml.), and a trace of mercuric oxide. The mixture was heated under reflux for 10 min., the excess of acid was neutralised, and a solution of sodium hydroxide (3 g.) in ethanol (10 ml.) was added; heating was continued for a further 2 hr. Isolation of the acid fraction gave *n*-hexanoic acid (2·0 g., 17%), b. p. 47°/0·03 mm., n_D^{17} 1·4187 (Simon, *Bull. Soc. chim. Belg.*, 1929, **38**, 47, gives b. p. 205°/760 mm., n_D^{15} 1·4188).

The Reaction Between Acetic Acid (2 Mol.) and Methoxyacetylene (1 Mol.).—Methoxyacetylene (2·8 g.) was added to frozen acetic acid (6·0 g.) during 20 min. with external cooling. The resultant mixture was stored at 0° for 1½ hr. and then at 20° for 18 hr. Careful fractionation

gave methyl acetate (2·5 g., 68%), b. p. 56°, n_D^{19} 1·3628, a small intermediate fraction, and acetic anhydride (4·3 g., 85%), b. p. 71—72°/70 mm., $n_D^{18\cdot5}$ 1·3906. (Literature values are b. p. 57° and n_D^{17} 1·3639 for methyl acetate; b. p. 68°/53 mm. and n_D^{20} 1·3896 for acetic anhydride.) The methyl acetate was characterised as methyl 3 : 5-dinitrobenzoate, m. p. 109°, and the acetic anhydride as acetanilide, m. p. 114—115°, both undepressed on admixture with authentic samples.

Butyric Anhydride.—Methoxyacetylene (2·8 g.) was added to butyric acid (8·8 g.) at 10°. The reaction was only mildly exothermic. After 16 hr. at 20° distillation gave: methyl acetate (2·3 g., 62%); butyric acid (*ca.* 1·0 g.), b.p. 72—73°/18 mm., n_D^{24} 1·3990 (Found: equiv., 84. Calc.: equiv., 88); and butyric anhydride (4·8 g., 61%), b. p. 91—92°/18 mm., n_D^{25} 1·4118 (Found: equiv., 77·5. Calc.: equiv., 79). (Whitby, *J.*, 1926, 1463, gives for butyric anhydride b. p. 198°, n_D^{18} 1·4143.) The anhydride reacted vigorously with aniline to give butyranilide, m. p. 96° (Robertson, *J.*, 1919, **115**, 1220, gives m. p. 96°).

Monochloroacetic Anhydride.—Monochloroacetic acid (9·5 g.) in tetrahydrofuran (10 ml.) was treated with methoxyacetylene (2·8 g.) at 15°. The reaction was exothermic and external cooling was required. The mixture, after 18 hr. at 15—20°, was distilled to give the anhydride, b. p. 118—120° (bath temp.)/0·05 mm. (Found: equiv., 85. Calc.: equiv., 85·5), which reacted with aniline to give the anilide (yield *ca.* 90%), m. p. 136°. (Bischoff and Walden, *Ber.*, 1894, **27**, 2949, give b. p. 110°/10 mm. for monochloroacetic anhydride; Meyer, *Ber.*, 1875, **8**, 1152, gives m. p. 135° for chloroacetanilide.)

Trichloroacetic Anhydride.—Trichloroacetic acid (1·4 g.) in methylene dichloride (4 ml.) was treated with methoxyacetylene (0·5 ml.). After 20 hr. at 20°, distillation gave the anhydride (0·86 g., 64%), b. p. 128° (bath temp.)/0·02 mm., $n_D^{20\cdot5}$ 1·5078 (Fichter, Fritsch, and Miller, *Helv. Chim. Acta*, 1923, **6**, 503, give b. p. 98—100°/11 mm.).

Heptanoic Anhydride.—Heptanoic acid (1·3 g.) was treated with methoxyacetylene (0·41 g.); after 20 hr. at 20° the mixture was distilled to give heptanoic anhydride (0·81 g., 67%), b. p. 145° (bath temp.)/0·01 mm., n_D^{20} 1·4341 (Kraft and Rosing, *Ber.*, 1900, **33**, 3576, give b. p. 165°/15 mm. and Lumsden, *J.*, 1905, **87**, 93, gives n_D^{15} 1·4335 for heptanoic anhydride).

Phenylacetic Anhydride.—Methoxyacetylene (0·5 ml.) was added to phenylacetic acid (1·4 g.) in methylene dichloride (2 ml.), the mixture was set aside at 20° for 18 hr., and the solvent was then removed to give phenylacetic anhydride (1·24 g., 96%), m. p. 72—72·5° after recrystallisation from light petroleum (b. p. 60—80°). A mixture with phenylacetic acid (m. p. 76—77°) had m. p. 51—60° (Anschutz, *Ber.*, 1887, **20**, 1391, gives m. p. 72·5° for phenylacetic anhydride).

β-*Phenylpropionic Anhydride.*—β-Phenylpropionic acid (1·50 g.) similarly gave its anhydride (0·75 g., 53%), b. p. 195° (bath temp.)/0·05 mm., n_D^{20} 1·5419; the anilide had m. p. 94—95° (Robinson and Shinoda, *J.*, 1925, **127**, 1976, give b. p. 216°/14 mm. for the anhydride. Dieckmann, Hoppe, and Stein, *Ber.*, 1904, **37**, 4627, give m. p. 96° for the anilide).

Pivalic Anhydride.—Methoxyacetylene (0·40 g.) was added to pivalic acid (1·0 g.) in ether (2 ml.) containing orthophosphoric acid (*ca.* 0·05 ml.). After 16 hr. at 20°, distillation gave pivalic anhydride (0·67 g., 75%), b. p. 103° (bath temp.)/15 mm., $n_D^{19\cdot5}$ 1·4104 (Greenwood, Whitmore, and Crooks, *J. Amer. Chem. Soc.*, 1938, **60**, 2028, give b. p. 124°/93 mm., n_D^{20} 1·4093). Treatment with aniline gave pivalanilide, m. p. 127—128° (Schwartz and Johnson, *J. Amer. Chem. Soc.*, 1931, **53**, 1005, give m. p. 128°).

Crotonic Anhydride.—Methoxyacetylene (0·5 ml.) was added portionwise to crotonic acid (0·85 g.) in methylene dichloride (2 ml.) containing a trace of mercuric oxide. After 20 hr. at 20° distillation gave the crude anhydride (0·62 g.), b. p. *ca.* 95° (bath temp.)/0·02 mm., n_D^{17} 1·466, which reacted exothermally with aniline to give crotonanilide, m. p. 115°, in good yield. (Luniak, *Ber.*, 1909, **42**, 915, gives b. p. 114°/12 mm., n_D^{20} 1·4745 for crotonic anhydride. Authenrieth and Speiss, *Ber.*, 1901, **34**, 189, give m. p. 115° for crotonanilide.)

Maleic Anhydride.—Maleic acid (1·1 g.) in methylene dichloride (3 ml.) was treated cautiously with ethoxyacetylene (1·0 ml.) in methylene dichloride (2 ml.) at 25—30°. A small amount of an insoluble white precipitate had formed after 1 hr. (polymer ?), which was discarded. Isolation gave maleic anhydride (0·88 g., 95%), m. p. 51—52° undepressed on admixture with an authentic sample of m. p. 53—54°.

Toluene-p-*sulphonic Anhydride.*—Methoxyacetylene (0·20 g.) was added to a suspension of toluene-*p*-sulphonic acid (0·85 g.) in methylene dichloride (5 ml.). A vigorous reaction took place and efficient cooling was required. Evaporation of the solvent and treatment with potassium hydrogen carbonate solution gave toluene-*p*-sulphonic anhydride (0·42 g., 52%), m. p. 122—124° (Meyer and Schlegl, *Monatsh.*, 1913, **34**, 573, give m. p. 122—125°).

2-*Methoxy*-2-*methyl*-4 : 6-*dioxo*-1 : 3-*dioxan.*—Methoxyacetylene (2·8 g.) in tetrahydrofuran

(5 ml.) was added to a solution of malonic acid (5·2 g.) in tetrahydrofuran (10 ml.). After 16 hr. at −5° removal of the solvent and distillation at 240° (bath temp.)/0·1 mm. yielded an oil (1·5 g.) and much acetic acid. Two redistillations gave *2-methoxy-2-methyl-4 : 6-dioxo-1 : 3-dioxan* (0·45 g., 6%), b. p. 85—95° (bath temp.)/0·1 mm., n_D^{24} 1·4345. Entirely satisfactory analytical data were not obtained (Found : C, 46·4, 45·9; H, 6·15, 6·45. $C_6H_8O_5$ requires C, 45·0; H, 5·03%). Light absorption : Maximum 2430 Å, ε = 782; after excess of sodium hydroxide had been added : Maximum 2700 Å, ε = 6330.

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Researches on Acetylenic Compounds. Part XLIV. The Reaction between Nickel Carbonyl and Some Esters of ω-Acetylenic Acids.*

By E. R. H. JONES, G. H. WHITHAM, and M. C. WHITING.

[Reprint Order No. 4928.]

Reaction of esters of ω-acetylenic acids with nickel carbonyl provides a simple route to half-esters of α-methylenedicarboxylic acids.

THE interaction of esters of ω-acetylenic acids (Eglinton and Whiting, *J.*, 1953, 3052) has now been studied, and a simple route to certain otherwise inaccessible half-esters thereby discovered :

$$\underset{\text{(I)}}{HC{\equiv}C{\cdot}[CH_2]_n{\cdot}CO_2Me} \xrightarrow{Ni(CO)_4} \underset{CO_2H \quad \text{(II)}}{H_2C{=}C{\cdot}[CH_2]_n{\cdot}CO_2Me} \xrightarrow{HO^-} \underset{CO_2H \quad \text{(III)}}{H_2C{=}C{\cdot}[CH_2]_n{\cdot}CO_2H}$$

Compounds of type (II) have previously been obtained only from the corresponding dicarboxylic acids. In contrast to these earlier methods, that now described yields only one of the two possible half-esters of (III), its structure being known without doubt.

The esters (I; n = 1, 2, 3, and 4) reacted smoothly with nickel carbonyl under the standard conditions (Jones, Shen, and Whiting, *J.*, 1950, 230) to give the products (II) in yields of 28—46%; on a larger scale the yields would probably approach 50%, since these were typical exothermal "Type *A*" reactions (*idem*, *J.*, 1951, 48). Hydrolysis converted the half-esters into the dicarboxylic acids (III), the first two members of which series were already known. Pent-4-ynoic acid itself, under the usual conditions, did not undergo exothermal reaction ("Type *B*"), though a small (5%) yield of the expected dicarboxylic acid was obtained. Hex-5-ynonitrile, on the other hand, underwent a normal exothermal reaction and gave the expected half-nitrile of (III; n = 3) in 40% yield; its infra-red spectrum indicated that the possible cyclisation to a glutarimide derivative had not taken place.

In the alkaline hydrolysis of (II; n = 1) under vigorous conditions, the itaconic acid formed was rearranged to mesaconic acid.

Nickel carbonyl did not react with ethyl propiolate under the usual conditions, a result in accordance with the empirical rules of Jones, Shen, and Whiting (*loc. cit.*, 1951). It might be expected that replacement of the ethoxycarbonyl group by the carbamoyl or $\cdot CO_2^-$ groupings, in which internal conjugation more effectively reduces the tautomeric effect of the carbonyl linkage, might permit reaction. With propiolamide no exothermal reaction occurred and no recognisable product was isolated; but when propiolic acid, in the presence of acetic acid and excess of sodium acetate (the dissociation constants of acetic and propiolic acids are $1{\cdot}8 \times 10^{-5}$ and $1{\cdot}4 \times 10^{-2}$, respectively) was treated with nickel carbonyl a quite unexpected product, *trans-trans*-muconic acid, was obtained in small yield. No precedent is known for a reductive coupling reaction of this type.

Light-absorption Properties.—The ultra-violet absorption spectra of the acids (III) are

* Part XLIII, preceding paper.

illustrated, together with that of mesaconic acid, in the Figure. Since simple α-alkylacrylic acids are difficult to purify, these results may be useful for comparison purposes; 95% ethanol was used in every case. Unfortunately the only recent and fairly extensive study of the absorption spectra of ethylenic acids (Ungnade and Ortega, *J. Amer. Chem. Soc.*, 1951, **73**, 1565) is, as the authors have recently pointed out (*idem*, 1952, **74**, 6313), largely invalidated as a result of scattered-light errors (cf. Eglinton, Jones, and Whiting, *J.*, 1952, 2873). The results reported confirm a general impression that, as with the corresponding ketones, an α-alkyl group displaces the maximum of acrylic acid less than a β-alkyl group, and are consistent with the present observation that the spectra of acids (III) show no maximum above 2060 Å; crotonic acid has $\lambda_{max.}$ 2035 Å, $\varepsilon = 14{,}600$. The well-defined inflection at 2400 Å is noteworthy (it seems to be general for αβ-ethylenic acids and esters), as is the much flatter curve found with mesaconic acid.

It has been pointed out recently (Freeman, *J. Amer. Chem. Soc.*, 1953, **75**, 1859) that α-methylene-acids do not show the strong absorption band at *ca.* 880 cm.$^{-1}$ associated with the simple $>C{=}CH_2$ grouping, but do absorb at 935—950 cm.$^{-1}$. The acid (III; $n = 3$) (in Nujol) and its dimethyl ester (in carbon disulphide) did show fairly strong bands at 959 cm.$^{-1}$ and 950 cm.$^{-1}$, respectively, but confirmation of its structure by ozonolysis (36% yield of formaldehyde) was considered necessary.

Experimental

Ethyl 3-Carboxybut-3-enoate.—Ethyl but-3-ynoate (6·5 g.), ethanol (30 c.c.), glacial acetic acid (3 c.c.), and water (1 c.c.) were stirred at 70°. A solution of nickel carbonyl (2 c.c.) in ethanol (15 c.c.) was added dropwise; an exothermal reaction began after a short induction period, and the temperature was maintained at 75° by controlling the rate of addition. After the solution had cooled, ether (50 c.c.) was added and all volatile material (b. p. <50°) was distilled off, the remaining solution was poured into dilute sulphuric acid, and the acid fraction was isolated with ether. Evaporation of the dried extract gave an oil which soon solidified; crystallisation from light petroleum (b. p. 30—40°)–ether gave the *half-ester* (2·8 g., 28%) as stout needles, m. p. 58—59° (Found: C, 52·75; H, 6·2. $C_7H_{10}O_4$ requires C, 53·15; H, 6·35%).

Itaconic Acid.—A solution of ethyl 3-carboxybut-3-enoate (0·5 g.), potassium hydroxide (1·0 g.), and water (20 c.c.) was set aside at 20° for 5 days. After evaporation of the ethanol and acidification the acid fraction was isolated by continuous extraction with ether; crystallisation from nitromethane gave needles (0·29 g., 71%), m. p. 167—168° (Delisle, *Annalen*, 1893, **269**, 87, gives m. p. 162—164°).

Mesaconic Acid.—Ethyl 3-carboxybut-3-enoate (1·0 g.) was heated under reflux with 50% potassium hydroxide (10 c.c.) for 30 min. Isolation of the acid fraction followed by recrystallisation from nitromethane gave the acid as small prisms, m. p. 199—200° (Fittig, *Annalen*, 1877, **188**, 73, gives m. p. 200°).

Ethyl 4-Carboxypent-4-enoate.—The reaction was carried out as above at 70° with ethyl pent-4-ynoate (12·6 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), water (1·5 c.c.), and a solution of nickel carbonyl (5 c.c.) in ethanol (15 c.c.). Isolation of the acid fraction with ether followed by distillation gave the *half-ester* (7·85 g., 46%), b. p. 100—102°/0·01 mm., $n_D^{19.5}$ 1·4575 (Found: C, 55·1; H, 7·05. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%), which solidified to a mass of needles, m. p. *ca.* 5°.

α-Methyleneglutaric Acid.—(i) Ethyl 4-carboxypent-4-enoate (2·6 g.) was hydrolysed by heating it under reflux with 50% aqueous potassium hydroxide (20 c.c.) for 30 min. Acidification followed by isolation with ether gave the acid (1·7 g., 81%), which crystallised from acetone–benzene as small prisms, m. p. 131—132° (von Pechmann, *Ber.*, 1903, **36**, 1202, gives m. p. 130—131°).

(ii) Pent-4-ynoic acid (4·9 g.), ethanol (30 c.c.), glacial acetic acid (3 c.c.), and water (1·5 c.c.) were heated at 70° while a solution of nickel carbonyl (3 c.c.) in ethanol (10 c.c.) was added in small portions during 15 min. No exothermal reaction took place; isolation of the acidic fraction with ether followed by crystallisation from acetone–benzene gave the acid (0·4 g., 5·5%) as small prisms, m. p. 132—133° undepressed on admixture with a specimen prepared by method (i).

Ethyl 5-Carboxyhex-5-enoate.—Ethyl hex-5-ynoate (10 g.), ethanol (30 c.c.), glacial acetic acid (5 c.c.), and water (1·5 c.c.) were treated at 70° with nickel carbonyl (3 c.c.) in ethanol (10 c.c.). Isolation of the acid fraction with ether followed by distillation gave the *half-ester*

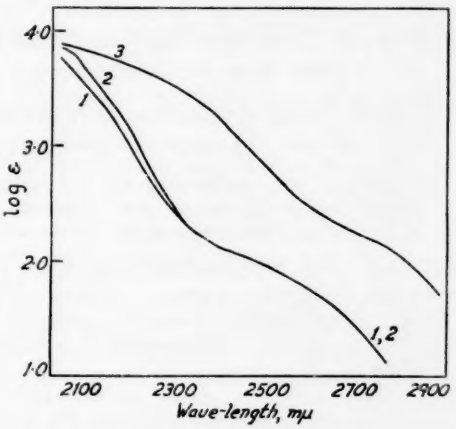
(5·3 g., 40%), b. p. 101—103°/0·01 mm., n_D^{17} 1.4608, which solidified to a mass of needles, m. p. 25—27° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 57·3; H, 7·3. $C_9H_{14}O_4$ requires C, 58·2; H, 7·6%).

α-Methyleneadipic Acid.—(i) Ethyl 5-carboxyhex-5-enoate (1·9 g.) was heated under reflux with 20% aqueous potassium hydroxide (20 c.c.) for 30 min. Acidification and isolation of the acid fraction with ether, followed by crystallisation from water, gave the *acid* (1·55 g., 96%) as minute prisms, m. p. 127—128·5° (Found: C, 52·6; H, 5·9. $C_7H_{10}O_4$ requires C, 53·1; H, 6·4%).

(ii) 1-Cyanopent-4-ene-4-carboxylic acid (1·35 g.; see below) was heated under reflux with 10% aqueous potassium hydroxide (20 c.c.) until evolution of ammonia ceased (4 hr.). Isolation of the acid fraction after acidification gave the acid (1·0 g., 65%), m. p. 127·5—128° after three crystallisations from water; the melting-point was undepressed on admixture with a specimen obtained from (i).

Ozonolysis of α-Methyleneadipic Acid.—A slow stream of ozonised oxygen was passed through a solution of the acid (0·38 g.) in acetic acid (40 c.c.) during 1 hr. The issuing gases were passed through water (30 c.c.). At the end of the reaction the aqueous and acetic acid solutions

1. *Itaconic acid.*
2. $CH_2{=}C(CO_2H)\cdot[CH_2]_4\cdot CO_2H$.
3. *Mesaconic acid.*



were mixed, saturated aqueous dimedone solution (100 c.c.) was added, and the solution was set aside at 0° for 48 hr. The formaldehyde derivative of dimedone was obtained as needles (0·26 g., 36%), m. p. 188—190° undepressed on admixture with an authentic specimen.

Ethyl Hex-5-ynoate.—This was prepared from hex-5-ynoic acid (Eglinton and Whiting, *loc. cit.*), ethanol, and sulphuric acid and had b. p. 67·5°/10 mm., n_D^{13} 1·4359 (Found: C, 68·6; H, 8·5; ·C≡CH, 17·55. $C_8H_{12}O_2$ requires C, 68·5; H, 8·65; ·C≡CH, 17·85%).

Ethyl 6-Carboxyhept-6-enoate (II, $n = 4$).—A mixture of ethyl hept-6-ynoate (5·1 g.), ethanol (30 c.c.), glacial acetic acid (2·5 c.c.), and water (1 c.c.) was treated with nickel carbonyl (2 c.c.) in ethanol (5 c.c.). Isolation of the acid fraction with ether followed by distillation gave the *half-ester* (2·4 g., 37%), b. p. 108—109°/0·02 mm., n_D^{16} 1·4602 (Found: C, 60·0; H, 8·05. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%).

α-Methylenepimelic Acid.—Ethyl 6-carboxyhept-6-enoate (1·0 g.), potassium hydroxide (1 g.), and water (20 c.c.) were shaken at 20° for 16 hr., and the mixture was then acidified. The acid fraction was isolated with ether; crystallisation from water gave the *acid* as needles (0·45 g., 53%), m. p. 88·5—89·5° (Found: C, 55·45; H, 7·05. $C_8H_{12}O_4$ requires C, 55·8; H, 7·05%).

1-Cyanopent-4-ene-4-carboxylic Acid.—A mixture of 1-cyanopent-4-yne (9·3 g.), ethanol (30 c.c.), glacial acetic acid (6 c.c.), and water (1·5 c.c.) was treated with a solution of nickel carbonyl (4 c.c.) in ethanol (15 c.c.). Isolation of the acid fraction with ether gave a pale yellow oil, and on distillation the fraction, b. p. 140—143°/1·5 mm., rapidly solidified. Crystallisation from carbon tetrachloride gave the *acid* as glistening plates (5·45 g., 39%), m. p. 58—61° (Found: C, 59·9; H, 6·45. $C_7H_9O_2N$ requires C, 60·4; H, 6·5%).

Reaction of Nickel Carbonyl and Sodium Propiolate.—A solution of nickel carbonyl (4 c.c.) in ethanol (10 c.c.) was added during 30 min. to a mixture of sodium propiolate (from propiolic

acid, 7 g.), ethanol (50 c.c.), glacial acetic acid (4 c.c.), and water (2·4 c.c.), maintained at 70°. No exothermal reaction occurred; isolation of the acid fraction with ether gave a yellow pasty mass, which on trituration with ethyl acetate, followed by filtration and crystallisation of the residue from water, gave *trans-trans*-muconic acid (70 mg., 1%) as clusters of needles, m. p. 295—300° (Elvidge, Linstead, Sims, and Orkin, *J.*, 1950, 2239, give m. p. 301°). The acid was heated under reflux with methanol (15 c.c.) and sulphuric acid (1 drop) during 1 hr. After cooling, filtration of the crystalline precipitate, and recrystallisation from methanol the ester was obtained as needles, m. p. 157—158°, undepressed on admixture with an authentic specimen (*idem, ibid.*) (Found: C, 56·1; H, 6·1. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%).

We thank Mr. E. S. Morton and Mr. H. Smith for microanalyses. One of us (G. H. W.) thanks the Department of Scientific and Industrial Research for a maintenance grant. We are grateful for the supply of nickel carbonyl by the Mond Nickel Co. Ltd.

THE UNIVERSITY, MANCHESTER. [*Received, December 28th*, 1953.]

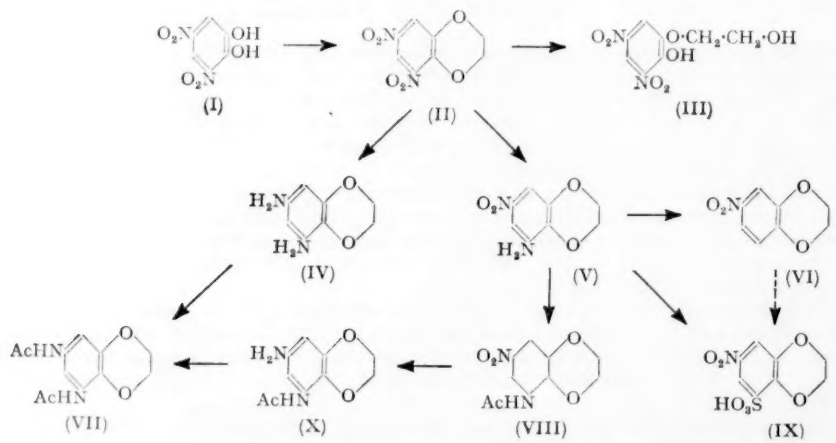
Derivatives of Benzo-1 : 4-dioxan. Part II. Some Compounds derived from 5 : 7-Dinitrobenzo-1 : 4-dioxan.*

By P. M. HEERTJES, (MISS) A. A. KNAPE, and H. TALSMA.

[Reprint Order No. 5068.]

Preparation and orientation of 5 : 7-dinitro-, 5-amino-7-nitro-, and 5 : 7-diamino-benzo-1 : 4-dioxan, and 7-nitrobenzo-1 : 4-dioxan-5-sulphonic acid, and some intermediates and derivatives are described.

THE reactions described in this paper are shown in the annexed chart; that marked with a broken arrow has already been recorded elsewhere. Most of the conversions were carried out in the usual way and they determine the orientation of all the compounds as those of 3 : 5-dinitropyrocatechol and 6-nitrobenzo-1 : 4-dioxan † are known. The following points merit mention.



The starting material, 5 : 7-dinitrobenzo-1 : 4-dioxan (II), had to be prepared indirectly *via* 3 : 5-dinitropyrocatechol (I), because no direct nitration method starting from benzo-1 : 4-dioxan has yet been found. Synthesis of 3 : 5-dinitropyrocatechol described very briefly by Nietzky and Moll (*Ber.*, 1893, **26**, 2182) and Kehrmann and Prunier (*Helv. Chim.*

* Part I, *J.*, 1954, 18. † Ring Index names and numbering are used.

Acta, 1924, **7**, 984) is detailed in the Experimental section and an improved hydrolysis of 3 : 5-dinitropyrocatechol monoacetate (cf. Baltzly and Buck, *J. Amer. Chem. Soc.*, 1941, **63**, 2022) has been found to give higher yields.

3 : 5-Dinitropyrocatechol has been converted into 5 : 7-dinitrobenzo-1 : 4-dioxan by the action of 1 : 2-dibromoethane in an alkaline solution of glycol on the analogy of the preparation of benzo-1 : 4-dioxan (Heertjes, Dahmen, and Wierda, *Rec. Trav. chim.*, 1941, **60**, 569). A by-product of this reaction had the composition $C_8H_8O_7N_2$, and was probably 2-2′-hydroxyethoxy-4 : 6-dinitrophenol (III), formed by hydrolysis of 5 : 7-dinitrobenzo-1 : 4-dioxan with water. This water results partly from the formation of the potassium salt of catechol, and partly from the decomposition of the dibromoethane with potassium carbonate, yielding vinyl bromide, water, and carbon dioxide.

5-Amino-7-nitrobenzo-1 : 4-dioxan (V) was diazotised and converted with sulphur dioxide and copper into the mononitro-monosulphinic acid, which was oxidised to 7-nitrobenzo-1 : 4-dioxan-5-sulphonic acid (IX), identical with that obtained by direct sulphonation of 6-nitrobenzo-1 : 4-dioxan (Heertjes and Revallier, *ibid.*, 1950, **69**, 262), but not previously oriented.

Experimental

M. p.s, and those recorded in Part I, are corrected.

3 : 5-*Dinitropyrocatechol* (I).—Pyrocatechol diacetate (75 g.; m. p. 62—63°; cf. Green, *J.*, 1927, 502) was gradually added to nitric acid (*d* 1·52; 400 ml.) which was stirred and cooled below −5°. The mixture was poured on ice shavings (3 kg.), and, after melting of the ice, the yellow precipitate of dinitropyrocatechol monoacetate was collected, washed with ice-water until free from acid, and dried (78 g., 82%; m. p. 123·8—124·6°). To obtain the 3 : 5-dinitropyrocatechol, the monoacetyl derivative was dissolved in methanol (450 ml.) and concentrated hydrochloric acid (5 ml.) and kept at room temperature (24 hr.); after evaporation of all the liquid the solid yellow residue was washed with water and dried at 110° (21 g., 98%; m. p. 166·0—166·5°).

5 : 7-*Dinitrobenzo*-1 : 4-*dioxan* (II).—3 : 5-Dinitropyrocatechol (20 g.) and anhydrous potassium carbonate (7 g.) in glycol (200 ml.) were heated at 50° until the evolution of carbon dioxide ceased and the liquid obtained had a dark red colour. Nitrogen was passed over the mixture throughout this and the following operations. 1 : 2-Dibromoethane (100 g.) was added and the mixture was gently refluxed (135°) till the colour changed to brown. Anhydrous potassium carbonate (*ca.* 2 g.) was added till the liquid became dark red again. This was repeated every time the colour changed to brown and stopped when on addition no change to a red was obtained (4—6 hr.). The mixture was then poured into water (2 l.). The precipitated 5 : 7-*dinitrobenzo*-1 : 4-*dioxan* (18 g., 80%) crystallised from acetone as faintly yellow needles, m. p. 145·5—145·7° (Found: N, 12·3, 12·4. $C_8H_6O_6N_2$ requires N, 12·4%).

The precipitate of 5 : 7-dinitrobenzo-1 : 4-dioxan was sometimes accompanied by a red crystalline substance, insoluble in boiling acetone. After extraction of the main product with acetone, this red substance was treated with dilute hydrochloric acid, yielding yellow (?)2-2′-*hydroxyethoxy*-4 : 6-*dinitrophenol*, which, crystallised from acetone and from water, had m. p. 155·7—156·0° (Found: C, 39·2; H, 3·3; N, 11·5. $C_8H_8O_7N_2$ requires C, 39·35; H, 3·3; N, 11·5%).

Boiling 5 : 7-dinitrobenzo-1 : 4-dioxan with aqueous potassium carbonate yielded also a red substance, which could be converted with dilute hydrochloric acid into the same yellow substance. For the preparation of 5 : 7-dinitrobenzo-1 : 4-dioxan this side reaction could be avoided by placing a water separator between the flask and the reflux condensor to keep the water content of the mixture as low as possible.

5-*Amino*-7-*nitrobenzo*-1 : 4-*dioxan* (V).—A fine suspension of 5 : 7-dinitrobenzo-1 : 4-dioxan (12 g.) in ethanol (100 ml.) was heated to 40°. Stannous chloride dihydrate (36 g.) in ethanol (36 ml.) and concentrated hydrochloric acid (36 ml.) was added dropwise at 40—60°. After a clear red-brown solution had been obtained, stirring was continued for another ½ hr. The mixture was poured into water (150 ml.), unchanged dinitro-compound was filtered off, and the filtrate treated with alkali until most of the tin compounds had redissolved. The remaining solid substance was collected and extracted with acetone. After removal of the acetone the *amine* crystallised in orange needles (5·7 g., 55%), m. p. 147·2—147·8 (from aqueous acetone, 1 : 1) (Found: N, 14·3, 14·35. $C_8H_8O_4N_2$ requires N, 14·3%).

Diazotizing the amine and boiling it with ethanol yielded a mononitro-compound, m. p.

118·2—119·4°. The mixed m. p. with 6-nitrobenzo-1 : 4-dioxan (VI) (m. p. 121—122°; cf. Heertjes, Dahmen, and Wierda, *Rec. Trav. chim.*, 1941, **60**, 569) was 119·6—121·4°. When 5-amino-7-nitrobenzo-1 : 4-dioxan (1·6 g.) was heated with acetic anhydride (8 ml.) for 15 min. and then cooled and diluted with water (40 ml.) the *acetamide* (VIII) separated and crystallised from acetone in faint pink needles, m. p. 234·9—235·4° (Found : N, 11·8, 11·9. $C_{10}H_{10}O_5N_2$ requires N, 11·8%).

5 : 7-*Diaminobenzo*-1 : 4-*dioxan* (IV).—5 : 7-Dinitrobenzo-1 : 4-dioxan (10·5 g.), suspended in ethanol (100 ml.), was hydrogenated in the presence of Raney nickel at room temperature. After removal of the catalyst and washing with ethanol, the filtrate was concentrated at diminished pressure to a small volume. The *diamine* (4·6 g., 60%) separated in white prisms, m. p. 109·6—110·3° (Found : N, 17·0, 16·9. $C_8H_{10}O_2N_2$ requires N, 16·9%). To the filtrate some drops of concentrated hydrochloric acid were added and by evaporation a second portion (2·6 g., 26%) of the amine was obtained as hydrochloride.

The *diacetyl* derivative (VII) was prepared by dissolving the free diamine in the calculated amount of acetic anhydride (exothermal reaction). After cooling, a thick syrup was obtained, which solidified slowly. Repeated crystallisation from water gave white needles, m. p. 203·0—203·3° (Found : N, 11·15, 11·3. $C_{12}H_{14}O_4N_2$ requires N, 11·2%).

5-*Acetamido*-7-*aminobenzo*-1 : 4-*dioxan* (X).—A suspension of 5-acetamido-7-nitrobenzo-1 : 4-dioxan (2 g.) in ethanol (70 ml.) was hydrogenated in the presence of Raney nickel at room temperature. During the reaction the product separated. It was dissolved by heating the mixture to the b. p. and the catalyst was removed by filtration of the hot solution. 5-*Acetamido*-7-*aminobenzo*-1 : 4-*dioxan* (1 g., 59%) crystallised, on cooling, in white feathers, m. p. 198·7—199·7° (from ethanol) (Found : N, 13·65, 13·7, 13·8. $C_{10}H_{12}O_3N_2$ requires N, 13·5%). Probably a small part has been hydrolysed. By acetylation the diacetyl derivative (VII) was formed.

7-*Nitrobenzo*-1 : 4-*dioxan*-5-*sulphinic Acid* (cf. Gattermann, *Ber.*, 1899, **32**, 1136).—5-Amino-7-nitrobenzo-1 : 4-dioxan (2·5 g.) in concentrated hydrochloric acid (7·5 ml.) and water (37·5 ml.) was diazotized with sodium nitrite (2 g.) in water (10 ml.) at 0°. The solution was added dropwise to ice-cooled water (50 ml.) which was saturated with sulphur dioxide and contained copper powder (17·5 g.) while sulphur dioxide was bubbling through this mixture. The solution and the precipitate were both extracted with ether. The extract was dried and the ether was removed. The sulphinic acid (0·5 g., 15%) remaining, after crystallisation from ether, had m. p. 135° (decomp.).

7-*Nitrobenzo*-1 : 4-*dioxan*-5-*sulphonic Acid* (IX).—A solution of the 5-sulphinic acid (0·43 g.), potassium permanganate (0·5 g.), and potassium carbonate (0·5 g.) in water (10 ml.) was heated at 100° (15 min.). The excess of potassium permanganate was then decomposed with ethanol, and the manganese oxide filtered off. After cooling, the white crystalline potassium sulphonate (0·4 g., 74%) was collected and washed with acetone.

The sulphonyl chloride was prepared by heating the potassium salt (0·3 g.) with phosphorus pentachloride (0·6 g.) at 150°/(15 min.). After cooling, the phosphorus oxychloride was decomposed with water. The white residue (0·24 g., 85%), after crystallisation from dilute acetic acid, had m. p. 169·4—170·8°. The sulphonic acid prepared by direct sulphonation of 6-nitrobenzo-1 : 4-dioxan (*loc. cit.*) was converted into a sulphonyl chloride, m. p. 170·6—171·4°, not depressed on admixture with this product.

Thanks are expressed to Mr. E. G. Kiel for his assistance with this work.

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*Chemistry of Pongamol. Part II.**

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[Reprint Order No. 5115.]

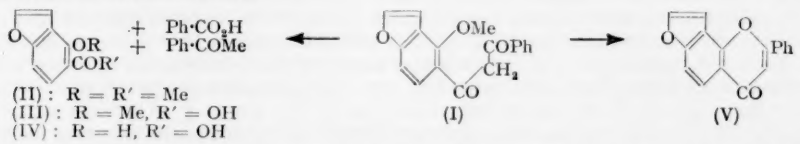
Pongamol, the second crystalline component of the seed oil of *Pongamia glabra*, is shown to be benzoyl-*O*-methylkaranjoylmethane (5-benzoylacetyl-4-methoxybenzofuran) (I) by a study of its fission with alkali and demethylation with hydriodic acid. It is the first example of a naturally occurring diketone related to flavones.

In Part I * pongamol was shown to have the molecular formula $C_{18}H_{14}O_4$ and to contain one methoxyl group. Though it gave a ferric chloride colour indicative of a phenolic or enolic hydroxyl group, it did not undergo methylation or benzoylation under ordinary conditions. Oxidation of pongamol with permanganate gave benzoic acid. Further, its colour reactions with concentrated sulphuric acid and with magnesium and hydrochloric acid were somewhat similar to those of karanjin, 3-methoxyfurano(2′ : 3′-7 : 8)flavone. It was believed therefore, that pongamol had a closely related structure.

Subsequently, fission of pongamol was carried out with aqueous-alcoholic potassium hydroxide. This gave a mixture which has now been analysed by paper-chromatography. The products were first separated into neutral and acid fractions. In the latter, benzoic acid was readily characterised, because of its higher solubility in water. The remaining portion consisted of a mixture of karanjic (IV) and *O*-methylkaranjic acid (III), which were largely separated by using the solubility difference in water but not fully purified. However, methylation afforded pure *O*-methylkaranjic acid. Obviously, the primary product of fission was this *O*-methylkaranjic acid and some of it suffered demethylation in alkali. The neutral fraction was also a mixture, consisting of acetophenone and a solid ketone, $C_{11}H_{10}O_3$, having one methoxyl group and giving no ferric reaction. That it was 5-acetyl-4-methoxybenzofuran (II) was confirmed by its conversion into *O*-methylkaranjic acid and its synthesis from *O*-methylkaranjoyl chloride and ethyl acetoacetate. This ketone, karanjic acid, and its methyl ether all give pronounced colours in concentrated sulphuric acid.

The fission is simpler with absolute methyl-alcoholic potassium hydroxide, yielding almost entirely benzoic acid and the ketone (II).

The results given above lead to the conclusion that pongamol is benzoyl-*O*-methylkaranjoylmethane (5-benzoylacetyl-4-methoxybenzofuran) (I), its degradations being represented as in the following scheme. In accordance with this structure, it gives a copper complex and a pronounced ferric chloride reaction and when demethylated undergoes ring-closure as discussed below.



(II) : R = R′ = Me
(III) : R = Me, R′ = OH
(IV) : R = H, R′ = OH

(I) (V)

In Part I, demethylation of pongamol by hydriodic acid and by aluminium chloride in benzene was reported. The former yielded a neutral product $C_{17}H_{12}O_4$. This demethylation with hydriodic acid has now been found to proceed best under milder conditions; the product which is nonphenolic and does not undergo acetylation or methylation is a monohydrate and the anhydrous substance agrees with the requirements for furano-(2′ : 3′-7 : 8)flavone (V), the simplest member of this group of furanoflavones and hitherto unknown. Demethylation by aluminium chloride in benzene cannot be simple because of the ability of benzene to add to the furan ring (Krishnaswami and Seshadri, *Proc. Indian Acad. Sci.*, **1942**, **15**, *A*, **437**).

* Part I, *Proc. Indian Acad. Sci.*, 1942, **15**, *A*, 419.

The elucidation of the constitution of pongamol is of importance in connection with the biogenesis of sap-soluble pigments. This structure, which is closely related to flavones, has not been found to occur in Nature before. Robinson's theory (*Nature*, 1936, **137**, 172; *Phil. Trans.*, 1939, **230**, *B*, 149) of the evolution of the C_{15} skeleton suggests a stage of this type. But normally when a free hydroxyl group is present in the *o*-position, the compound would undergo ring-closure. In pongamol, an earlier stage of methylation has rendered this diketone stable.

A matter of further significance is the occurrence of pongamol and karanjin together, both being methylation products, but belonging to different types. Clearly, when the methylation mechanism of the plant functions, the nuclear hydroxyl group in pro-pongamol (pyrone ring open) is methylated whereas in pro-karanjin it is protected by chelation so that the second hydroxyl group is methylated instead, flavone ring-closure being the final stage.

As a structure analogous to pongamol should be mentioned eugenone (Meijer and Schmid, *Helv. Chim. Acta*, 1948, **31**, 1603), which is 2 : 4 : 6-trimethoxybenzoylacetone, a diketone related to the chromones and present in *Eugenia caryophyllata*. Here too stability has been conferred on it by the methylation of the *o*-hydroxyl groups.

Experimental

Pongamol was extracted directly from the seeds of *Pongamia glabra*. A modified purification will be described elsewhere. When an ethereal solution of pongamol was shaken with saturated aqueous copper acetate the ethereal layer became green and a yellowish-green precipitate was formed at the interface. When crystallised from chloroform–ether, this copper complex melted at 226—227°.

Fission with Aqueous-alcoholic Potassium Hydroxide.—Pongamol (0·75 g.), dissolved in alcohol (38 c.c.), was treated with aqueous potassium hydroxide (2·8 g. in 56 c.c.). The clear yellow solution was refluxed on a water-bath for 3 hr., the solution becoming turbid. Alcohol was distilled off as completely as possible. The distillate gave a copious precipitate with 2 : 4-dinitrophenylhydrazine; the product crystallised from alcohol as fine needles, m. p. 239° alone or mixed with acetophenone 2 : 4-dinitrophenylhydrazone. The aqueous alkaline solution was acidified with sulphuric acid and extracted with ether and the ethereal solution extracted successively with aqueous sodium hydrogen carbonate and aqueous sodium hydroxide, the latter removing very little. Examination of the ethereal residue (C) is reported below.

A portion of the carbonate extract (A) was acidified and extracted with ether. Circular paper-chromatography of the whole of the extracted acid showed the presence of three components (R_F, at 23°, 0·61, 0·56, and 0·51; solvent, *n*-butanol saturated with ammonia) when bromophenol-blue (0·04% in alcohol) was used as the indicator, and of one component giving a blue ring (R_F 0·61) with ferric chloride (1% solution in alcohol). The R_F values of karanjic, *O*-methylkaranjic, and benzoic acid were found to be 0·61, 0·56, and 0·51 respectively.

The bulk of the carbonate extract (A) was acidified and the solid (B) (0·25 g.) was filtered off. This gave a blue colour with alcoholic ferric chloride, a colourless solution with concentrated sulphuric acid becoming blue when warmed (pure karanjic and *O*-methylkaranjic acids gave a similar colour reaction with sulphuric acid), m. p. 126° with sintering at 96°. It was boiled with water, most of it dissolving. The insoluble part was filtered off and washed with hot water to remove the more soluble partion completely; it then crystallised from dilute alcohol as colourless needles which sintered at 196° and melted at 206° (decomp.); the m. p. of karanjic acid is 218° (decomp.). It gave a blue colour with alcoholic ferric chloride and a negative test for methoxyl. The hot aqueous filtrate, when kept in the refrigerator, gave a crystalline solid which after another crystallisation from hot water formed rectangular tablets, m. p. 142—144°; the m. p. of *O*-methylkaranjic acid is 148°. It still gave a blue ferric reaction and contained 13% of methoxyl (*O*-methylkaranjic acid requires OMe, 16·1%). The filtrate from (A) was extracted with ether; the colourless residue obtained on removal of the ether was crystallised twice from water, forming colourless plates, m. p. 120°, identical with benzoic acid.

From the remaining ethereal solution (C) the solvent was distilled off. The oily residue of *5-acetyl-4-methoxybenzofuran* solidified and crystallised from light petroleum as rectangular tablets, m. p. 59° (0·19 g.). These gave no colour with alcoholic ferric chloride and dissolved in concentrated sulphuric acid to a yellow solution becoming green when warmed (Found: C, 69·2; H, 5·5; OMe, 15·6. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3; OMe, 16·3%). It gave a 2 : 4-dinitrophenylhydrazone crystallising from alcohol as stout needles and rectangular rods, m. p. 221°.

When the fission was carried out by boiling for 8 hr., the yield of the component (karanjic acid) insoluble in hot water was greater.

Methylation of the Acid Fraction (*B*).—The acid fraction (B) (0·1 g.) was heated in a small volume of dry acetone with excess of methyl iodide (0·2 c.c.) and anhydrous potassium carbonate (0·2 g.) under reflux for 45 hr. The solution was filtered and, after removal of the acetone, water was added and the mixture extracted with ether. The extract was evaporated and the residue boiled with 25% aqueous sodium hydroxide (2 c.c.) until clear. After acidification with hydrochloric acid, the precipitate was crystallised from hot water, giving *O*-methylkaranjic acid as colourless rectangular plates, m. p. 148° (no colour with alcoholic ferric chloride; R_F 0·56).

Fission with Absolute Methanolic Potassium Hydroxide.—Pongamol (0·2 g.) was heated with methyl-alcoholic potassium hydroxide (0·4 g. in 6 c.c.) under reflux for about 8 hr. As much of the alcohol as possible was then distilled off and the residue treated with water. After cooling in ice, the solid product (II) was filtered off. On crystallisation from light petroleum it had m. p. and mixed m. p. 59° (yield 85 mg.). When the aqueous alkaline solution was acidified with hydrochloric acid only a small precipitate was obtained, giving a positive ferric reaction. It was filtered off and the solution extracted with ether, which yielded benzoic acid.

Oxidation of the Ketone (II) *to O-Methylkaranjic Acid.*—A solution of the ketone (0·15 g.) and iodine (0·2 g.) in pyridine (1 c.c.) was heated on a water-bath for 1 hr.; a crystalline product separated. The mixture was kept in the refrigerator before the solid was filtered off. The solid was heated on a water-bath with 2% aqueous potassium hydroxide (8 c.c.) for 45 min., then the whole was cooled and acidified with hydrochloric acid. The precipitate was dissolved in aqueous sodium hydrogen carbonate and reprecipitated with acid; it then crystallised from hot water as rectangular plates, m. p. 148° alone or mixed with *O*-methylkaranjic acid, m. p. 148°; it gave no ferric reaction.

Synthesis of 5-Acetyl-4-methoxycoumarone (II).—*O*-Methylkaranjic acid (Seshadri and Venkateswarlu, *Proc. Indian Acad. Sci.*, 1941, **13**, *A*, 407) (1 g., 1 mol.) and thionyl chloride (5 c.c.) were refluxed on a water-bath for 1 hr. Excess of chloride was removed under reduced pressure. The residue was treated with dry carbon tetrachloride and again distilled to remove the last traces of thionyl chloride. A viscid mass remained. Ethyl acetoacetate (0·8 g., 1·2 mols.) was added to finely granulated sodium (0·25 g., 2·2 mols.) in anhydrous ether (10 c.c.) and shaken. After about 1 hr. the acid chloride was added in dry ether (15 c.c.). The mixture was kept overnight, then boiled for 4 hr. It was treated first with ether and then with water. The ethereal layer, on evaporation, gave a liquid product which was mixed with water (8 c.c.); 10% aqueous potassium hydroxide (9 c.c.) was then added gradually during 2 hr. The clear mixture was gently boiled for 2 hr., cooled, and extracted with ether; the ethereal extract yielded the benzofuran as rectangular plates and tablets (from light petroleum), m. p. and mixed m. p. 60° (Found: C, 69·1; H, 5·3%) giving a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 221°.

Demethylation of Pongamol [*Furano*(2′ : 3′-7 : 8)*flavone* (V)].—Pongamol (0·5 g.) was dissolved in acetic anhydride (8 c.c.) and cooled in ice, and hydriodic acid (*d* 1·7; 8 c.c.) was added carefully. The mixture was heated for 40 min. at 115° and poured into aqueous sodium hydrogen sulphite. The brown solid product was crystallised twice from aqueous alcohol, forming woolly needles (0·31 g.), m. p. 146° (sinters at 115°; dehydration). *Furano*(2′ : 3′-7 : 8)*flavone* gave no colour with ferric chloride and did not dissolve in aqueous sodium hydroxide. It dissolved in concentrated sulphuric acid giving a yellow solution which became deep blue when warmed (Found, in a sample dried at 110° for 4 hr.: C, 77·5; H, 3·9. $C_{17}H_{10}O_3$ requires C, 77·8; H, 3·8%). An alcoholic solution gave an orange colour with magnesium and hydrochloric acid.

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Acetylenic Compounds related to "Agropyrene."

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1-Phenyloct-3-yn-2-ol was dehydrated to 1-phenyloct-1-en-3-yne. Sodium acetylide and β-phenylpropaldehyde gave 5-phenylpent-1-yn-3-ol (accompanied by 2-benzyl-5-phenylpent-2-enal). Attempted *C*-methylation of the pentynol gave only 3-methoxy-5-phenylpent-1-yne. Propynylmagnesium bromide and β-phenylpropaldehyde afforded 1-phenylhex-4-yn-3-ol, converted (either *via* 4-bromo-6-phenylhex-2-yne or directly) into 1-phenylhex-2-en-4-yne. This exhibits the properties of a conjugated vinylacetylene, and differs from "agropyrene."

Only one naturally occurring propyne derivative ("carlina oxide," 1-2′-furyl-3-phenylprop-1-yne; Rupe, Pfau, and Plattner, *Helv. Chim. Acta*, 1934, **17**, 372) was known up to 1947, when the discovery of an acetylenic hydrocarbon ("agropyrene") in the roots of *Agropyrum repens* was announced by Treibs (*Chem. Ber.*, 1947, **80**, 97) who assigned to it the structure 1-phenylhex-2-en-4-yne (I) on the basis of oxidative degradation and hydrogenation.

As a model substance 1-phenyloct-3-yn-2-ol (II) was prepared from phenylacetaldehyde and hexynylmagnesium bromide. In the ultra-violet it showed end-absorption at 2140 Å and a low-intensity maximum at 2600 Å, similar to the spectra of substituted benzyl alcohols (Braude, Jones, and Stern, *J.*, 1947, 1087).

$CH_3 \cdot C{:}C \cdot CH{:}CH \cdot CH_2Ph$ (I) $\quad Bu^n \cdot C{:}C \cdot CH(OH) \cdot CH_2Ph$ (II) $\quad Bu^n \cdot C{:}C \cdot CH{:}CHPh$ (III)

Dehydration by potassium hydrogen sulphate (Kuhn and Wallenfels, *Ber.*, 1938, **71**, 1889) gave 1-phenyloct-1-en-3-yne (III) which showed ultra-violet absorption maxima at 2200 and 2830 Å, at the same positions as, but with lower intensities than, the phenylbutadiene chromophore (Braude, Jones, and Stern, *loc. cit.*). Catalytic hydrogenation (platinum) afforded 1-phenyloctane, while semihydrogenation (palladium) gave 1-phenylocta-1 : 3-diene. This exhibited high-intensity absorption at 2240 and 2820 Å, in agreement with the behaviour recorded for phenylbutadiene (*idem, ibid.*); its instability was noted and, in common with these authors' experience, difficulty was encountered in obtaining correct analyses for carbon.

Condensation of sodium acetylide with β-phenylpropaldehyde was next examined. This aldehyde has been prepared in unstated yield from calcium β-phenylpropionate and calcium formate (Miller and Rohde, *Ber.*, 1890, **23**, 1080); use of the barium salts, not previously reported, gave a 7% yield only. Oxidation of 3-phenylpropan-1-ol by chromic–sulphuric acid between 20° and 50° gave 10—20% of aldehyde, accompanied by 3-phenylpropyl β-phenylpropionate, which was the main product (53%) at 10—15°. Preparation of esters by oxidation of alcohols is well known (*e.g.*, Reilly and Hickinbottom, *Proc. Roy. Soc. Dublin*, 1921, **16**, 246) but under the mild conditions employed the mechanism is probably oxidation of an intermediate hemiacetal rather than formation and subsequent esterification of the acid, as postulated by these authors.

The action of ethyl orthoformate on phenethylmagnesium bromide gave the desired aldehyde (41%) which with sodium acetylide in liquid ammonia afforded 5-phenylpent-1-yn-3-ol (IV) by steam-distillation from the bisulphite compound of the unchanged aldehyde, fractional distillation having failed to separate aldehyde and alcohol; distillation of the involatile residue gave 2-benzyl-5-phenylpent-2-enal (V), formed by aldol condensation.

Treatment of the dimagnesium bromide complex of (IV) with methyl iodide or toluene-*p*-sulphonate did not achieve the desired *C*-methylation, and the action of methyl sulphate on the disodium salt gave 3-methoxy-5-phenylpent-1-yne. No reaction occurred between (IV) and hydrochloric acid (Campbell, Campbell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882) at room temperature. Thionyl chloride afforded 77·5% of 3-chloro-5-phenylpent-1-yne, which was dehydrohalogenated in hot pyridine, estimation of chloride ion produced showing elimination of 75% of the chlorine in 3 hours. Distillation, however, gave 25% of

chloro-compound as sole product; a similar treatment occupying 4 hours gave 17% of chloro-compound, and in both cases much ether-insoluble tar was produced.

Condensation of β-phenylpropaldehyde with sodiopropyne in liquid ammonia (Vaughn, Hennion, Vogt, and Nieuwland, *J. Org. Chem.*, 1937, **2**, 1) gave the required 1-phenylhex-4-yn-3-ol (VI) in only 7% yield. This alcohol showed light absorption of low intensity at

$CH{\equiv}C{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2Ph$ (IV) $\quad CH_2Ph{\cdot}CH_2{\cdot}CH{:}C(CH_2Ph){\cdot}CHO$ (V) $\quad CH_3{\cdot}C{\equiv}C{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2Ph$ (VI)

$CH_3{\cdot}C{\equiv}C{\cdot}CHCl{\cdot}CH_2{\cdot}CH_2Ph$ (VII) $\quad [CH_3{\cdot}C{\equiv}C{\cdot}CH(CH_2{\cdot}CH_2Ph){\cdot}]_2O$ (VIII)

2550 Å and end-absorption at 2170 Å. Other products obtained were (V) and 1 : 8-diphenyloct-4-yn-3 : 5-diol, which was partly dehydrated at its boiling point (200—220°/0·15 mm.) as shown by analysis.

The Grignard method readily gave 1-phenylhex-4-yn-3-ol (VI) in 53% yield. This failed to react with hydrochloric acid but thionyl chloride gave 4-chloro-6-phenylhex-2-yne (VII), accompanied by an equal quantity of di-(1-phenethylbut-2-ynyl) ether (VIII), produced either by self-etherification during the reaction with thionyl chloride (cf. Heilbron, Jones, and Weedon, *J.*, 1945, 81) or during the distillation from chloro-compound and unchanged alcohol. As attempted dehydrochlorination of the chloro-compound was unsuccessful, 4-bromo-6-phenylhex-2-yne (cf. VII) was prepared by the method of Henbest, Jones, and Walls (*J.*, 1949, 2690). It showed only end-absorption in the ultra-violet. Dehydrobromination with diethylaniline resulted in a 44% yield of 1-phenylhex-2-en-4-yne (I), which exhibited light absorption in accordance with the conjugated vinylacetylene chromophore, and on hydrogenation gave 1-phenylhexane, identified by analysis and physical constants.

The physical constants obtained for (I) ($n_D^{26\cdot5}$ 1·5510, $d^{26\cdot5}$ 0·9450) differed considerably from those reported (n_D^{20} 1·5695, d^{20} 0·9744) by Treibs (*loc. cit.*) for "agropyrene." Treibs states that the molecular refraction (calc. 52·6; found 52·4) shows an absence of exaltation, and therefore excludes the structure of a conjugated phenylhexa-1 : 3 : 5-triene but not that of (I), which he accordingly assigns to "agropyrene."

Vinylacetylene compounds do, however, show an exaltation of the molecular refraction, ranging from 1·1 to 1·6 units (see Johnson, "The Chemistry of the Acetylenic Compounds," Vol. I, E. Arnold, London, 1946) when refractions are calculated by using for the carbon–carbon triple bond either Eisenlohr's value (2·398; *Z. physikal. Chem.*, 1910, **75**, 604) or that of Auwers (2·325 for terminal and 2·573 for non-terminal acetylenes; *Ber.*, 1935, **68**, 1635). However, re-calculation of the molecular refractivities of 17 vinylacetylenes (Anzilotti and Vogt, *J. Amer. Chem. Soc.*, 1939, **61**, 572) from the recent data of Jeffery and Vogel (*J.*, 1948, 674) and Vogel (*J.*, 1948, 1842) employing the values of 2·35 for non-terminal and 1·977 for terminal acetylenic bonds, gave the figures shown in Table 1; the exaltation produced by the vinylacetylene grouping thus has an average magnitude of 1 unit.

Calculation of the molecular refraction of (I) with the same figures gave a value of 52·02; the molecular refraction of synthetic (I) was 52·82, corresponding to an exaltation of 0·8 unit, in reasonable agreement with that observed for other vinylacetylene compounds. Treibs's value (52·4) for "agropyrene" implies an exaltation of 0·38 unit; no spectrographic data were published by him, nor has it so far been possible to obtain details of the ultra-violet spectrum of natural "agropyrene."

Dehydration of 1-phenylhex-4-yn-3-ol with potassium hydrogen sulphate gave a 36% yield of (I), possessing properties in excellent agreement with those of the material obtained from the bromo-compound. In the preparation of (I) by dehydration or dehydrobromination, the normal reaction is one of *trans*-elimination requiring hydroxyl or bromine, the two carbon atoms, and hydrogen to lie in one plane for elimination to take place (Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093). The synthetic product (which can in this case possess either a *cis*- or a *trans*-ethylenic structure) is, from stability considerations, probably the *trans*-olefin. Irradiation of a solution of synthetic (I) with ultra-violet light caused a 33% diminution in the intensity of the absorption maxima at 2280 and

2340 Å, with the simultaneous appearance of a new low intensity maximum at 2850 Å. On storage of the irradiated solution in the dark partial reversion was noted, the intensities of these maxima reaching 75% of the original values. This behaviour is characteristic of photo-conversion of the *trans*- into *cis*-isomer, which then reverts to the *trans*-form (cf.,

TABLE 1.—*Ultra-violet absorption in 95% ethanol.*

Substance	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$	Substance	$\lambda_{max.}$ (Å)	$\varepsilon_{max.}$
1-Phenyloct-3-yn-2-ol (II)	2600	250	1-Phenyloct-1-en-3-yne (III) ...	2200	15,750
	2150 *	2,950		2230 †	15,250
				2830	16,250
1-Phenylhex-4-yn-3-ol (VI)	2490	500		2950	11,500
	2540	550		2150 *	16,000
	2590	550			
	2170 *	3,100	1-Phenylocta-1 : 3-diene	2240	14,500
				2330	9,000
1-Phenylbut-2-en-1-ol [1]	2510	450		2710	19,000
	2580	450		2820	25,000
				2860	20,000
4-Bromo-6-phenylhex-2-yne (cf. VII)	2220 *	3,400		3030	6,000
			1-Phenylbuta-1 : 3-diene [1]	2230	12,000
1-Phenylhex-2-en-4-yne (I)	2280	15,200		2330	8,500
	2350 †	14,500		2710	28,000
	2550 †	800		2800	28,300
				2900	27,000
Dec-3-en-5-yn-2-ol [2]	2260	16,000		3050	6,000
	2350 †	15,000			

* End absorption. † Inflexion.

[1] Braude, Jones, and Stern, *J.*, 1947, 1087. [2] Heilbron, Jones, and Raphael, *J.*, 1943, 264.

TABLE 2.—*Molecular refraction of vinylacetylenic compounds.*

Substance	$[R_L]_D$ Found	$[R_L]_D$ Calc.	Exaltation	Substance	$[R_L]_D$ Found	$[R_L]_D$ Calc.	Exaltation
Hex-5-en-3-yn-2-ol	30·20	29·21	0·99	Hept-1-en-3-yne	33·04	32·28	0·76
5-Methylhex-5-en-3-yn-1-ol ...	34·73	33·86	0·87	Oct-1-en-3-yne...	38·33	36·93	1·40
Hept-6-en-4-yn-3-ol	34·31	,,	0·45	Non-1-en-3-yne	42·97	41·58	1·39
5-Methylhex-5-en-3-yn-2-ol ...	34·85	,,	0·99	Dec-1-en-3-yne...	47·02	46·22	0·80
2-Methylhex-5-en-3-yn-2-ol ...	34·96	,,	1·10	Dodec-1-en-3-yne	56·18	55·52	0·66
Oct-7-en-5-yn-4-ol	39·32	38·51	0·81	Non-2-en-4-yne	42·67	41·58	1·09
3-Ethylhept-6-en-4-yn-3-ol ...	44·17	43·15	1·02	Dec-2-en-4-yne...	47·57	46·22	1·35
1-(But-3-en-1-ynyl)*cyclo*hexanol	46·57	45·59	0·98				
3-*n*-Propyloct-7-en-5-yn-4-ol ...	53·44	52·45	0·99	Average exaltation : 0·97			
5-Methyltridec-1-en-3-yn-5-ol...	67·36	66·40	0·86				

inter al., Cook, Jones, and Polya, *J.*, 1939, 1315; Sandoval and Zechmeister, *J. Amer. Chem. Soc.*, 1947, **69**, 553.) Many naturally occurring compounds possess a *cis*-ethylenic structure and it is possible that " agropyrene " is the *cis*-isomer of (I). The molecular refractions observed by Campbell and Eby (*J. Amer. Chem. Soc.*, 1941, **63**, 2684) for seven pairs of *cis*- and *trans*-olefins show the *trans*-isomer, in every case, to have a value for $[R_L]_D$ (on the average) 0·14 unit higher than that of the corresponding *cis*-compound. The effect of *cis–trans*-isomerism on the magnitude of the exaltation in a vinylacetylene system does not appear to have been investigated.

It is evident that (I) and " agropyrene " differ appreciably and further work is necessary before a structure can be assigned with certainty to the natural hydrocarbon.

EXPERIMENTAL

1-Phenyloct-3-yn-2-ol.—A solution of hexynylmagnesium bromide, prepared from hex-1-yne (18 g.) and ethylmagnesium bromide (from 4·5 g. of magnesium) in ether (200 c.c.) by the method of Cymerman, Heilbron, and Jones (*J.*, 1944, 146), was treated gradually with a solution of phenylacetaldehyde (15 g.) in ether (100 c.c.) at 0° with vigorous stirring. After 5 hours' refluxing, the complex was worked up with ice-cold ammonium chloride solution and ether. Distillation of the dried (Na_2SO_4) extracts gave *1-phenyloct-3-yn-2-ol* (21 g., 84%) as a pleasant-smelling liquid, b. p. 145—148°/1·6 mm., 150—151°/2·3 mm., n_D^{25} 1·5184 (Found: C, 83·3; H, 9·0%; active H, 1·05. $C_{14}H_{18}O$ requires C, 83·15; H, 8·95%). Light absorption: See

Table 1. The *α-naphthylurethane*, formed after 1 week at 20°, crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 71—72° (Found : N, 4·05. $C_{25}H_{25}O_2N$ requires N, 3·8%).

1-Phenyloct-1-en-3-yne.—A mixture of 1-phenyloct-3-yn-2-ol (3 g.) and freshly powdered anhydrous potassium hydrogen sulphate (2·2 g.) was heated at 190° (bath) for 1 hr. at 35 mm. Dehydration set in at 175°, and distillation of the residue afforded *1-phenyloct-1-en-3-yne* (1·5 g., 56%) as a pale yellow mobile liquid, b. p. 144—146°/2 mm., 130—134°/1 mm., $n_D^{20\cdot5}$ 1·5613 (Found : C, 90·9; H, 8·8. $C_{14}H_{16}$ requires C, 91·25; H, 8·75%). Light absorption : See Table 1. Quantitative hydrogenation : A solution of 1-phenyloct-1-en-3-yne (1·15 g.) in methanol (50 c.c.) was shaken with platinic oxide (10 mg.) and hydrogen till absorption ceased, 448 c.c. (21°/763 mm.), of hydrogen were absorbed, equiv. to 3·0 double bonds. Removal of catalyst and distillation of the residue afforded 1-phenyloctane (1 g., 90%) as a pleasant-smelling mobile liquid, b. p. 260—261°/759 mm., n_D^{20} 1·4889 (Eisenlohr and Schulz, *Ber.*, 1924, **57**, 1815, give b. p. 264°, and Schmidt, Hopp, and Schoeller, *ibid.*, 1939, **72**, *B*, 1893, give n_D^{20} 1·4851).

1-Phenylocta-1 : 3-diene.—A solution of 1-phenyloct-1-en-3-yne (2·25 g.) in methanol (50 c.c.) was shaken with 10% palladised charcoal (0·5 g.) and hydrogen until 1 mol. had been absorbed. Filtration and distillation gave *1-phenylocta-1 : 3-diene* as a mobile sweet-smelling liquid (2 g., 89%), b. p. 126—130°/0·9 mm., $n_D^{27\cdot5}$ 1·5430, which rapidly darkened and resinified (Found : C, 88·7; H, 9·75. $C_{14}H_{18}$ requires C, 90·15; H, 9·85%). Light absorption : See Table 1.

β-Phenylpropaldehyde.—(*a*) Ethyl orthoformate (72·5 g.) was added slowly with stirring to a solution of phenethylmagnesium bromide (from 14·9 g. of magnesium) in ether (100 c.c.) and the mixture then refluxed for 6 hr. Working-up by Bachman's method (*J. Amer. Chem. Soc.*, 1933, **55**, 4281) gave β-phenylpropaldehyde (27 g., 41%), b. p. 106—107°/12 mm., $n_D^{17\cdot5}$ 1·5280. Steam-distillation of the aldehyde bisulphite solution before addition of sodium hydrogen carbonate gave ethylbenzene (3·4 g., 6%), b. p. 136°/760 mm., n_D^{19} 1·4956 (lit., b. p. 136°, n_D^{20} 1·4951).

(*b*) Dry distillation of an intimate mixture of finely powdered barium β-phenylpropionate (97 g.) and barium formate (76 g.), finally *in vacuo*, afforded a yellow oil which was shaken with saturated sodium hydrogen sulphite solution. Isolation as described above gave the aldehyde (2·2 g., 7% yield on acid which reacted), b. p. 113—115°/23 mm., n_D^{18} 1·5275. The residue from the dry distillation gave recovered β-phenylpropionic acid (14·2 g., 28%), m. p. 47°.

3-Phenylpropyl β-Phenylpropionate.—A solution of chromium trioxide (33 g.) in sulphuric acid (100 c.c., 50% v/v) was added to a solution of 3-phenylpropanol (68 g.) in acetone (100 c.c.) with stirring, the temperature being kept at 10—15°. After a further 15 minutes' stirring, water (500 c.c.) and ether were added. Evaporation of the washed (water and sodium hydrogen carbonate solution) and dried (Na_2SO_4) ethereal extracts and distillation through a column packed (15 cm.) with single-turn helices gave β-phenylpropaldehyde (2·7 g., 4%), b. p. 45°/0·01 mm., n_D^{22} 1·5240, and *3-phenylpropyl β-phenylpropionate* (35·5 g., 53%) as a pleasant-smelling oil, b. p. 132—135°/0·01 mm., n_D^{20} 1·5408 (Found : C, 80·3; H, 7·65. $C_{18}H_{20}O_2$ requires C, 80·55; H, 7·5%). Alkaline hydrolysis gave β-phenylpropionic acid, m. p. and mixed m. p. 47·5—48·5°, and 3-phenylpropanol, b. p. 119°/12 mm., n_D^{25} 1·5357 (lit., b. p. 119°/12 mm., n_D^{20} 1·5356).

5-Phenylpent-1-yn-3-ol.—A stirred solution of sodium acetylide (from 9·2 g. of sodium) in liquid ammonia (500 c.c.), prepared by Jones and McCombie's method (*J.*, 1942, 733), was treated with β-phenylpropaldehyde (26·8 g.) in ether (25 c.c.) during ¾ hr. and the mixture stirred and cooled for a further 4¾ hr. After addition of ammonium chloride (14·7 g.), the ammonia was allowed to evaporate overnight, and the mixture decomposed with 2N-sulphuric acid and ice, and extracted with ether. The residue on evaporation of the washed (sodium hydrogen carbonate) ethereal extracts was shaken with a solution of sodium hydrogen sulphite (21 g.) in water (50 c.c.). Steam-distillation and ether-extraction of the distillate afforded *5-phenylpent-1-yn-3-ol* (11·8 g., 38%) as a sweet-smelling oil, b. p. 92—94°/0·4 mm., n_D^{17} 1·5344 (Found : C, 82·15; H, 7·6%; active H, 1·9. $C_{11}H_{12}O$ requires C, 82·45; H, 7·55%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 90—100°) as prisms, m. p. 97—97·5° (Found : N, 4·65. $C_{22}H_{19}O_2N$ requires N, 4·25%). Quantitative hydrogenation : The alcohol (0·8 g.) in methyl acetate (50 c.c.), shaken with platinic oxide (25 mg.) and hydrogen until absorption ceased, absorbed 223 c.c. of hydrogen at 15°/747 mm. (1·95 double bonds). Removal of catalyst gave 1-phenylpentan-3-ol, b. p. 52—56°/0·08 mm., n_D^{16} 1·5165.

Steam-distillation of the residual aldehyde bisulphite compound after addition of sodium hydrogen carbonate gave recovered β-phenylpropaldehyde (0·6 g., 2%), b. p. 117—119°/28 mm., n_D^{18} 1·5275. Ether-extraction of the residue not volatile in steam afforded *2-benzyl-5-phenylpent-2-enal* as a viscous oil (1 g., 2%), b. p. 175—180°/0·5 mm., n_D^{18} 1·5761 (Found : C, 86·0; H, 7·6. $C_{18}H_{18}O$ requires C, 86·35; H, 7·25%). It gave a positive reaction with Schiff's re-

agent and the 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as red needles, m. p. 165·5—166·5° (Found : N, 13·15. $C_{24}H_{22}O_4N_4$ requires N, 13·05%).

3-*Methoxy*-5-*phenylpent*-1-*yne*.—A solution of 5-phenylpent-1-yn-3-ol (4 g.) in ether (5 c.c.) was added dropwise with stirring to sodamide (2·2 g.) and ether (50 c.c.), and the mixture refluxed until evolution of ammonia had ceased (3½ hr.). Methyl sulphate (3·2 g.) in ether (10 c.c.) was added to the cooled mixture, which was refluxed for 1 hr. After addition of water, removal of solvent from the washed (dilute aqueous ammonia and water) and dried (Na_2SO_4) ethereal extracts gave 3-*methoxy*-5-*phenylpent*-1-*yne* (3 g., 68%) as a sweet-smelling mobile liquid, b. p. 66°/0·3 mm., $n_D^{23·5}$ 1·5031 (Found : C, 82·2; H, 8·4%; active H at 90°, 1·05. $C_{12}H_{14}O$ requires C, 82·65; H, 8·15%). It gave a positive test with Tollens's reagent.

3-*Chloro*-5-*phenylpent*-1-*yne*.—Freshly distilled thionyl chloride (6·7 g.) was added to a stirred solution of 5-phenylpent-1-yn-1-ol (8 g.) in pyridine (4·4 g.) at 50—60°, which temperature was maintained for a further 3 hr. The mixture was poured on ice (100 g.) and extracted with ether. Removal of solvent from the washed (dilute sulphuric acid, water, and sodium hydrogen carbonate) and dried (Na_2SO_4) extracts afforded 3-*chloro*-5-*phenylpent*-1-*yne* (6·9 g., 77·5%) as a pleasant-smelling liquid, b. p. 73—75°/0·25 mm., n_D^{24} 1·5292 (Found : C, 73·6; H, 6·5. $C_{11}H_{11}Cl$ requires C, 73·95; H, 6·2%).

1-*Phenylhex*-4-*yn*-3-*ol*.—(*a*) A solution of sodium acetylide (from 25 g. of sodium) in liquid ammonia (1 l.) was treated with methyl iodide (142 g.) in ether (150 c.c.) during 45 min. with further stirring and cooling for 4 hr. The prop-1-yne was converted into the sodium salt by addition of a suspension of sodamide (from 25 g. of sodium ; Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120) in liquid ammonia (700 c.c.). After a further hour's stirring, β-phenylpropaldehyde (147 g.) was added and the mixture stirred and cooled for 24 hr. Working-up with ammonium chloride (50 g.) and ether gave, on distillation, 2 fractions : (i) 1-*Phenylhex*-4-*yn*-3-*ol* (12 g., 7%) as a pleasant-smelling oil, b. p. 74—76°/0·05 mm., n_D^{22} 1·5349 (Found : C, 82·3; H, 8·0. $C_{12}H_{14}O$ requires C, 82·65; H, 8·15%). Light absorption : See Table 1. The α-*naphthylurethane* crystallised from light petroleum (b. p. 90—100°) as prisms, m. p. 103·5—105° (Found : C, 80·35; H, 6·1; N, 4·6. $C_{23}H_{21}O_2N$ requires C, 80·45; H, 6·1; N, 4·15%). (ii) 2-Benzyl-5-phenylpent-2-enal (25 g., 15%), as a viscous oil, b. p. 135—138°/0·05 mm., $n_D^{26·5}$ 1·5724. The 2 : 4-dinitrophenylhydrazone had m. p. 164—166°, undepressed on admixture with the sample (m. p. 165·5—166·5°) described above.

(*b*) A stream of prop-1-yne, prepared from 1 : 2-dibromopropane (395 g.), *n*-butanol (900 c.c.), and potassium hydroxide (450 g.) by the method of Heisig and Davis (*J. Amer. Chem. Soc.*, 1935, **57**, 339), was passed into a solution of ethylmagnesium bromide (from 12 g. of magnesium) in ether (200 c.c.) at 0°, and the mixture stirred for 6 hr. under a reflux condenser cooled to −40°. A solution of β-phenylpropaldehyde (67 g.) in ether (100 c.c.) was then added and the solution refluxed for 3 hr. The complex was decomposed (ammonium chloride solution) and acidified (10% sulphuric acid), and the ethereal extracts were washed with sodium hydrogen sulphite and sodium hydrogen carbonate solutions and dried (Na_2SO_4). Distillation gave 1-phenylhex-4-yn-3-ol (46 g., 53%), b. p. 88—90°/0·06 mm., n_D^{22} 1·5350.

4-*Chloro*-6-*phenylhex*-2-*yne*.—Addition of thionyl chloride (6·7 g.) to a solution of 1-phenylhex-4-yn-3-ol (8·5 g.) in pyridine (4·4 g.) at 40—50° and working up by the method described above gave 4-*chloro*-6-*phenylhex*-1-*yne* (2·5 g., 26%), as a sweet-smelling mobile liquid, b. p. 31—32°/0·05 mm., n_D^{25} 1·5230 (Found : C, 74·35; H, 6·9. $C_{12}H_{13}Cl$ requires C, 74·75; H, 6·75%), and *di*-(1-*phenethylbut*-2-*ynyl*) *ether* (2·5 g.) as a colourless oil, b. p. 114—118°/0·05 mm., $n_D^{25·5}$ 1·5407 (Found : C, 86·85; H, 7·9. $C_{24}H_{26}O$ requires C, 87·3; H, 7·9%).

4-*Bromo*-6-*phenylhex*-2-*yne*.—Freshly distilled phosphorus tribromide (30 g.,) in ether (30 c.c.) was added dropwise with stirring to a mixture of 1-phenylhex-4-yn-3-ol (17·4 g.) in ether (50 c.c.) and pyridine (1 g.) at −20° during 0·5 hr. The solution was allowed to come to room temperature and stirred for a further hour. Working up gave 4-*bromo*-6-*phenylhex*-2-*yne* (15 g., 65%), b. p. 78—80°/0·04 mm., n_D^{25} 1·5613 (Found : C, 61·1; 5·65. $C_{12}H_{13}Br$ requires C, 60·8; H, 5·5%). Light absorption : See Table 1.

1-*Phenylhex*-2-*en*-4-*yne*.—(*a*) A mixture of 4-bromo-6-phenylhex-2-yne (5 g.) and diethylaniline (15 c.c.) was heated at 160—170° (bath) for 15 min. under nitrogen and immediately cooled to 0°. The mixture was taken up in ether, washed with 2N-nitric acid, aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Distillation of the ethereal extracts gave 1-*phenylhex*-2-*en*-4-*yne* (1·4 g., 44%) as a sweet-smelling mobile liquid, b. p. 40°/0·04 mm., $n_D^{26·5}$ 1·5510, $d^{26·5}$ 0·9450 (Found : C, 91·85; H, 8·1; $[R_L]_D$ 52·82. $C_{12}H_{12}$ requires C, 92·25; H, 7·75%; $[R_L]_D$ 52·02). Light absorption : See Table 1. Addition of silver nitrate to the aqueous layer gave 3·1 g. (82%) of silver bromide. 1-Phenylhex-2-en-4-yne (0·425 g.) in methanol

(30 c.c.) was shaken with platinic oxide (20 mg.) and hydrogen until absorption ceased, 201 c.c. of hydrogen being absorbed at 26°/756 mm., equiv. to 3·0 double bonds. The catalyst was filtered off and the filtrate on distillation gave 1-phenylhexane (0·4 g., 94%) as a sweet-smelling liquid, b. p. 80—83°/1 mm., n_D^{22} 1·4880, d^{22} 0·8600 (Found: C, 89·1; H, 11·4; $[R_L]_D$ 54·28. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%; $[R_L]_D$ 54·25). Schmidt, Hopp, and Schoeller, *loc. cit.*, give b. p. 97·5—101°/12 mm., n_D^{20} 1·4868, d^{20} 0·8592, and Vogel (*J.*, 1948, 607) gives b. p. 222·5°/766 mm., n_D^{20} 1·4874, d^{20} 0·8602.

(*b*) A mixture of 1-phenylhex-4-yn-3-ol (6·2 g.) and powdered potassium hydrogen sulphate (5·3 g.) was heated at 190° (bath) for 30 min. at 45 mm. in a slow stream of nitrogen. Distillation gave the crude hydrocarbon (3 g.) still containing a trace of alcohol. Fractionation through a Vigreux column (10 cm.) gave 1-phenylhex-2-en-4-yne (2 g., 36%), b. p. 78—82°/0·3 mm., n_D^{16} 1·5532 (Found: C, 91·95; H, 8·0. Calc. for $C_{12}H_{12}$: C, 92·25; H, 7·75%). Light absorption: Max. at 2280 (ε 14,800), infl. at 2340 (ε 14,000) and 2550 Å (ε 600). The hydrocarbon (0·907 g.) in methanol (50 c.c.) was shaken with platinic oxide (30 mg.) and hydrogen until absorption ceased, 413 c.c. being absorbed at 18°/755 mm., corresponding to 2·95 double bonds. Filtration and distillation of the filtrate gave 1-phenylhexane (0·85 g., 94%), b. p. 104°/13 mm., n_D^{20} 1·4877, as a sweet-smelling liquid.

An alcoholic solution of the hydrocarbon containing 0·001 g./100 c.c. was irradiated in a quartz cell with ultra-violet light from a mercury-vapour lamp for 0·5 hr., and the spectrum then re-determined. The solution was then left in the dark for 0·5 hr. and the absorption again measured. The results are tabulated.

	Intensity (ε) at maxima (Å)		
Solution	2280	2340	2850
Original solution	14,900	14,250	—
After irradiation	9,500	10,000	1250
After storage in dark	11,250	11,000	1250

Absorption spectra were determined in 95% alcoholic solution by means of a Beckman quartz spectrophotometer, model DU. We are indebted to the late Mrs. E. Bielski for microanalyses.

UNIVERSITY OF SYDNEY. [*Received, October 19th*, 1953.]

Naphthyridines. Part I. The Chemistry of 1 : 5-*Naphthyridine.*

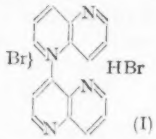
By E. P. HART.

[Reprint Order No. 5079.]

Amination of 1 : 5-naphthyridine has afforded 2-amino-1 : 5-naphthyridine. Use of bromine in chloroform gave the quaternary salt (I), which in water at 100° gave 4-hydroxy-1 : 5-naphthyridine and 1 : 5-naphthyridine. Oxidation of 1 : 5-naphthyridine with peracetic acid afforded the 1-oxide and 1 : 5-dioxide, converted by phosphoryl chloride into mono- and di-chloro-1 : 5-naphthyridine respectively, the dichloro-compound being characterised by conversion into the dianilino-derivative. Mono- and di-chloro-1 : 5-naphthyridine with toluene-*p*-sulphonhydrazide gave adducts, which decomposed in alkali to give 1 : 5-naphthyridine.

THERE are theoretically six isomeric naphthyridines (diazanaphthalenes) formed by the fusion of two pyridine nuclei, but only the 1 : 5- and the 1 : 8-isomers have been reported, otherwise than as derivatives (Allen, *Chem. Reviews*, 1950, **47**, 275). Moreover, no chemistry of the naphthyridine system itself, except hydrogenation of 1 : 5-naphthyridine (Miyaki, *J. Pharm. Soc. Japan*, 1942, **62**, 257), is recorded although a considerable amount of synthetic work, leading to naphthyridine derivatives, has been published (see particularly Ochiai and Miyaki, *Ber.*, 1937, **70**, 2081; 1941, **74**, 1115; *J. Pharm. Soc. Japan*, 1938, **58**, 764; Miyaki, *loc. cit.*; Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204; Petrow and Sturgeon, *J.*, 1949, 1157; Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224; Albert and Hampton, *J.*, 1952, 4985). It seemed therefore that a study of the syntheses and chemistry of the naphthyridine bases would be of interest. In this paper are recorded some reactions of 1 : 5-naphthyridine.

The base was prepared by the method of Bobranksi and Sucharda (*Ber.*, 1927, **60**, 1081; *Roczn. Chem.*, 1927, **7**, 241), who do not record the yield; Hauser and Reynolds (*loc. cit.*) record 27%. In the present work the yield has been raised by using a shorter reaction time. Attempted nitration, with a range of concentrated and fuming acids, gave unchanged starting material. Bromine in cold chloroform gave, in high yield, the quaternary 1-(1 : 5-naphthyridin-4-yl)-1 : 5-naphthyridinium bromide hydrobromide (I), hydrolysed



(I)

(II)

in water at 100° to 1 : 5-naphthyridine and 4-hydroxy-1 : 5-naphthyridine. The latter compound has been prepared by decarboxylation of 4-hydroxy-1 : 5-naphthyridine-2 : 3-dicarboxylic acid (Bobranski and Sucharda, *loc. cit.*) and from 3-aminopyridine by the ethoxymethylenemalonic ester method (Adams, Bradsher, Breslow, Amore, and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1317); in the present work it was prepared by a Skraup reaction on 3-amino-4-hydroxypyridine. 1 : 5-Naphthyridine with sodamide in liquid ammonia at room temperature afforded 2-amino-1 : 5-naphthyridine (II; R = NH_2, R′ = H), whence nitrous acid yielded 2-hydroxy-1 : 5-naphthyridine (II; R = OH, R′ = H). This was identical with the hydroxynaphthyridine obtained by Petrow and Sturgeon's method (*loc. cit.*) from a Skraup reaction on 5-amino-2-hydroxypyridine; the structure of (II; R = OH, R′ = H) is thus established.

Treatment of 1 : 5-naphthyridine with hydrogen peroxide in acetic acid solution gave the 1 : 5-dioxide. By the use of peracetic acid (Byers and Hickinbottom, *J.*, 1948, 286) the degree of oxidation could be controlled to produce the 1 : 5-dioxide and the 1-oxide. Only one instance of *N*-oxide formation in the naphthyridine series is recorded in the literature (Petrow and Sturgeon, *loc. cit.*). These compounds are of biological interest because of their resemblance to the quinoxaline *N*-oxides (McIlwain, *J.*, 1943, 322; Landquist, *J.*, 1953, 2816). Phosphoryl chloride and the monoxide gave 2-chloro-1 : 5-naphthyridine (II; R = Cl, R′ = H), which on hydrolysis afforded 2-hydroxy-1 : 5-naphthyridine. The 1 : 5-dioxide under similar conditions afforded a dichloro-1 : 5-naphthyridine to which the 2 : 6-structure is assigned, by analogy with the product from the monoxide. For dichloro-1 : 8-naphthyridine, conversion into the dihydrazino-derivative and subsequent treatment with nitrous acid to form a bistetrazolo-derivative established the orientation (Seide, *Ber.*, 1926, **59**, 2465); in the present work repeated attempts to obtain the dihydrazino-derivative failed. Hydrolysis of 2 : 6-dichloro-1 : 5-naphthyridine gave 2 : 6-dihydroxy-1 : 5-naphthyridine (II; R = R′ = OH). The dianilino-derivative was prepared by heating 2 : 6-dichloro-1 : 5-naphthyridine with aniline.

The method used by Albert and Royer (*J.*, 1949, 1148) for the removal of active chlorine atoms from the acridine nucleus was applied to 2-chloro- and 2 : 6-dichloro-1 : 5-naphthyridine, and in both cases yielded adducts which decomposed in alkali, forming 1 : 5-naphthyridine.

1 : 5-Naphthyridine and its 1 : 5-dioxide were found by Dr. A. T. Fuller not to be notably active against *Streptococcus haemolyticus*, *Staphylococcus aureus*, and *B. coli*.

Experimental

All extracts were dried with anhydrous sodium sulphate.

1 : 5-*Naphthyridine*.—3-Aminopyridine (*Org. Synth.*, **30**, 3) (15 g.), anhydrous glycerol (60 g.), arsenic acid (20 g.), and concentrated sulphuric acid (55 g.) were heated to 170° (oil-bath). Vigorous ebullition occurred, after which the temperature was kept at 170° for 2 hr. The mixture was then treated by Bobranski and Sucharda's method (*loc. cit.*). 1 : 5-Naphthyridine, pale yellow needles, m. p. 72° (7·5 g., 36%), separated from light petroleum (b. p. 40—60°) (Found: N, 21·4. Calc. for $C_8H_6N_2$: N, 21·5%).

1-(1 : 5-*Naphthyridin*-4-*yl*)-1 : 5-*naphthyridinium Bromide Hydrobromide* (I).—To a solution of 1 : 5-naphthyridine (0·4 g.) in chloroform (3 ml.) was slowly added, with stirring, bromine

(0·1 ml.) in chloroform (3 ml.). After a short time yellow crystals (0·6 g.) separated. Recrystallisation from alcohol afforded the yellow *quaternary salt*, m. p. 260—262° (Found: C, 45·2; H, 3·0; N, 13·4; Br, 37·9. $C_{16}H_{12}N_4Br_2$ requires C, 45·6; H, 2·9; N, 13·4; Br, 38·0%).

4-*Hydroxy*-1 : 5-*naphthyridine*.—(*a*) The quaternary salt (0·15 g.) was refluxed in water (10 ml.) for 2 hr. The clear solution was basified with potassium hydroxide, concentrated, and extracted with ether (2 × 20 ml.). Removal of solvent gave 1 : 5-naphthyridine, m. p. and mixed m. p. 72°. Acidification of the aqueous extract, evaporation to dryness, and extraction of the residue with hot alcohol gave 4-hydroxy-1 : 5-naphthyridine, colourless prisms, m. p. and mixed m. p. 340°.

(*b*) 3-Amino-4-hydroxypyridine (2·5 g.) (prepared by Dr. E. Tittensor), glycerol (6 g.), arsenic acid (3 g.), and concentrated sulphuric acid (10 g.) were heated together to 160° (oil-bath). Violent ebullition occurred, after which the temperature was kept at 160° for 2 hr. The cooled melt was extracted with concentrated hydrochloric acid (2 × 40 ml.), filtered, and basified with potassium hydroxide. The precipitated solids were collected and recrystallised from alcohol (charcoal). 4-Hydroxy-1 : 5-naphthyridine (1·2 g., 37%) separated as colourless prisms, m. p. 340° (sinter at 325°) (Found: N, 19·6. Calc. for $C_8H_6ON_2$: N, 19·2%).

2-*Amino*-1 : 5-*naphthyridine*.—Sodium (0·1 g.) was added to a solution of ammonium nitrate (0·1 g.) in liquid ammonia (40 ml.). After the sodium had reacted, 1 : 5-naphthyridine (0·4 g.) was added, and the mixture was set aside until the ammonia had evaporated. Sodium hydroxide solution (20%; 5 ml.) was stirred with the residue, needles of the amino-base (0·35 g.) separating. The picrate, recrystallised from water, formed yellow needles, m. p. 270° (Miyaki, *loc. cit.*, gives m. p. 272°) (Found: N, 22·0. Calc. for $C_8H_7N_3,C_6H_3O_7N_3$: N, 22·4%). The amino-base, on treatment with nitrous acid, did not couple with β-naphthol to give a coloured product.

2-*Hydroxy*-1 : 5-*naphthyridine*.—The amino-base (0·2 g.) in dilute hydrochloric acid (10 ml.) was treated dropwise with sodium nitrite (0·2 g.) in water (10 ml.). Nitrous fumes were removed by boiling, and the solution was concentrated to small volume. 2-Hydroxy-1 : 5-naphthyridine crystallised from alcohol as colourless needles, m. p. 256° alone or mixed with hydroxynaphthyridine prepared by Petrow and Sturgeon's method (*loc. cit.*) (Found: N, 19·7%).

1 : 5-*Naphthyridine* 1-*Oxide*.—1 : 5-Naphthyridine (0·2 g.) and 1·2M-peracetic acid (1·3 ml.) were heated at 55° for 20 hr. The brown mixture was cooled in ice, basified with potassium hydroxide, and extracted with chloroform (3 × 15 ml.). Removal of solvent gave a yellow mixture of mono- and di-oxide. Crystallisation from *cyclo*hexane gave 1 : 5-*naphthyridine* 1-*oxide* (0·05 g.) as a waxy solid, m. p. 125—127° (Found: C, 65·1; H, 4·2. $C_8H_6ON_2$ requires C, 65·6; H, 4·1%).

1 : 5-*Naphthyridine* 1 : 5-*Dioxide*.—(*a*) 1 : 5-Naphthyridine (0·2 g.) and 1·2M-peracetic acid (4·0 ml.) were heated at 55° for 20 hr., an exothermic reaction being at first observed. The clear yellow mixture was cooled in ice, basified with potassium hydroxide, and extracted with chloroform (3 × 15 ml.). Removal of solvent gave yellow crystals (0·2 g., 80%). 1 : 5-*Naphthyridine* 1 : 5-*dioxide* separated from alcohol as yellow clusters, m. p. 299—301° (Found: C, 58·7; H, 4·0; N, 17·5. $C_8H_6O_2N_2$ requires C, 59·2; H, 3·7; N, 17·3%).

(*b*) 1 : 5-Naphthyridine (0·2 g.) in glacial acetic acid (5 ml.) was treated with hydrogen peroxide (100-vol.; 2 ml.) and heated at 50° for 20 hr. Treatment as in the previous oxidation gave yellow clusters (0·2 g.), m. p. 299—301°.

2-*Chloro*-1 : 5-*naphthyridine*.—1 : 5-Naphthyridine 1-oxide (0·05 g.), phosphoryl chloride (2 ml.), and phosphorus pentachloride (0·1 g.) were gently heated to the b. p. and kept at this temperature for 20 min. The cooled mixture was stirred with ice and aqueous ammonia, and the precipitated solids were collected (0·04 g.). Crystallisation from the minimum volume of alcohol (charcoal) gave 2-chloro-1 : 5-naphthyridine as white needles, m. p. and mixed m. p. 112° (Found: N, 17·5; Cl, 21·4. Calc. for $C_8H_5N_2Cl$: N, 17·0; Cl, 21·6%).

2 : 6-*Dichloro*-1 : 5-*naphthyridine*.—1 : 5-Naphthyridine 1 : 5-dioxide (0·15 g.) was added to phosphoryl chloride (4 ml.), cooled in ice. The mixture was refluxed for 20 min., cooled, and poured on ice and aqueous ammonia. The precipitated solids (0·1 g.) were collected and recrystallised from light petroleum (b. p. 40—60°), yielding 2 : 6-*dichloro*-1 : 5-*naphthyridine* as colourless plates, m. p. 236—238° (Found: C, 47·9; H, 1·8; N, 13·9; Cl, 36·1. $C_8H_4N_2Cl_2$ requires C, 48·3; H, 2·0; N, 14·1; Cl, 35·6%).

2 : 6-*Dihydroxy*-1 : 5-*naphthyridine*.—The above dichloro-compound (50 mg.) was suspended in 10% sodium carbonate solution (5 ml.) and refluxed for 2 hr.; evaporation to dryness and extraction of the residue with hot methyl alcohol afforded 2 : 6-*dihydroxy*-1 : 5-*naphthyridine*, colourless clusters, subliming without melting *ca.* 360° (Found: C, 59·5; H, 3·0; N, 17·1.

$C_8H_6O_2N_2$ requires C, 59·2; H, 3·7; N, 17·3%). This gave no colour with ferric chloride solution.

2 : 6-*Dianilino*-1 : 5-*naphthyridine*.—The above dichloro-compound (30 mg.) and aniline (0·1 ml.) were heated at the b. p. for 5 min. and then on the water-bath for 1 hr. Excess of aniline was removed in steam, and the residue recrystallised from light petroleum (b. p. 40—60°). The *dianilino*-derivative separated as yellow prisms, m. p. 278° (Found: C, 76·3; H, 5·1. $C_{20}H_{16}N_4$ requires C, 76·9; H, 5·2%).

Adducts from Chloronaphthyridines.—(*a*) Saturated chloroform solutions of 2-chloro-1 : 5-naphthyridine and toluene-*p*-sulphonhydrazide (Albert and Royer, *loc. cit.*) were mixed, no precipitate forming until dry hydrogen chloride was passed into the mixture. 2-(N′-*Toluene*-p-*sulphonhydrazino*)-1 : 5-*naphthyridine dihydrochloride* separated as colourless needles (Found, by titration: Cl, 18·2. $C_{15}H_{16}O_2N_4SCl_2$ requires Cl, 18·4%). This salt had an indefinite m. p. giving a yellow residue.

(*b*) 2 : 6-Dichloro-1 : 5-naphthyridine, under similar conditions, afforded 2 : 6-*di*-(N′-*toluene*-p-*sulphonhydrazino*)-1 : 5-*naphthyridine dihydrochloride* (Found: Cl, 12·3. $C_{22}H_{24}O_4N_6S_2Cl_2$ requires Cl, 12·4%).

These adducts (0·1 g.) were heated in 10% sodium hydroxide solution (5 ml.). After evolution of nitrogen had ceased, extraction with ether gave yellow needles of 1 : 5-naphthyridine, m. p. and mixed m. p. 72°.

I am indebted to Dr. E. Tittensor for his interest and advice, and to Dr. J. Walker (National Institute for Medical Research) for kindly arranging for the biological tests. This work was in part aided by a grant from the Research Fund of the Chemical Society.

THE TECHNICAL COLLEGE, NOTTINGHAM. [*Received, January 30th*, 1954.]

Deoxyribonucleosides and Related Compounds. Part IV. The Configuration at the Glycosidic Centre in Deoxyadenosine and Deoxycytidine.*

By W. ANDERSEN, D. H. HAYES, A. M. MICHELSON, and A. R. TODD.

[Reprint Order No. 5091.]

Toluene-*p*-sulphonylation of 3′-acetyl-2′-deoxyadenosine yields 3′-acetyl-2′-deoxy-5′-toluene-*p*-sulphonyladenosine, which is readily converted into a *cyclo*nucleoside salt in hot acetone. It follows that deoxyadenosine has the β-configuration at the glycosidic centre, *i.e.*, it is 9-(2-deoxy-β-D-ribofuranosyl)-adenine. 5′-Acetyl-2′-deoxy-3′-toluene-*p*-sulphonyladenosine does not yield a *cyclo*nucleoside salt when heated.

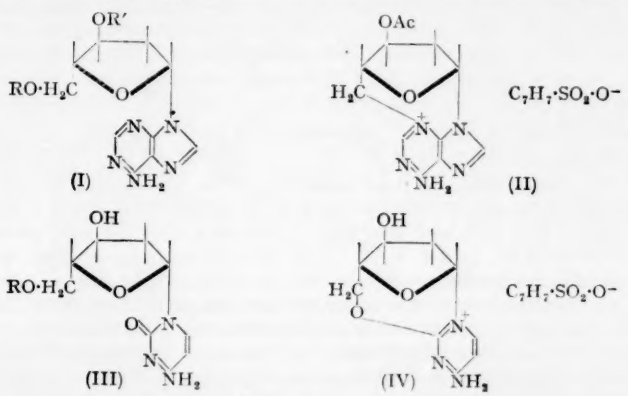
When 2′-deoxy-5′-toluene-*p*-sulphonylcytidine is heated in acetone, it appears also to form a *cyclo*nucleoside salt, but the latter is so unstable that it could not be isolated. The evidence of *cyclo*nucleoside salt formation is taken to indicate that deoxycytidine is also a β-glycoside.

THE structure of the ribonucleosides (adenosine, guanosine, uridine, and cytidine) derived from natural ribonucleic acids is fully established. They are all β-D-ribofuranosides of the respective purine or pyrimidine bases (Davoll, Lythgoe, and Todd, *J.*, 1946, 833; Clark, Todd, and Zussman, *J.*, 1951, 2952) and their synthesis has been effected (Howard, Lythgoe, and Todd, *J.*, 1947, 1052; Davoll, Lythgoe, and Todd, *J.*, 1948, 967, 1685; Kenner, Taylor, and Todd, *J.*, 1949, 1620). Less is known with certainty about the natural deoxyribonucleosides (deoxyadenosine, deoxyguanosine, thymidine, deoxycytidine, and 5-methyldeoxycytidine). That they are 2-deoxy-D-ribofuranosides of the corresponding purine and pyrimidine bases has been established (Brown and Lythgoe, *J.*, 1950, 1990; Dekker and Elmore, *J.*, 1951, 2864), and the attachment of the sugar residue at $N_{(9)}$ in the purine and at $N_{(3)}$ in the pyrimidine nucleosides has been inferred from spectroscopic evidence (Gulland and Story, *J.*, 1938, 259, 262). No evidence bearing on the stereochemistry at the glycosidic centre has been advanced, nor has any one of them as yet been synthesised.

* Part III, *J.*, 1951, 2230.

The periodate oxidation method used to establish the β-configuration at the glycosidic carbon atom in the ribonucleosides (Davoll, Lythgoe, and Todd, *J.*, **1946**, 833) cannot be applied to the deoxyribonucleosides since these substances contain no α-glycol system. Clark, Todd, and Zussman (*loc. cit.*) provided independent proof of the β-configuration of the ribonucleosides by showing that the 5′-*p*-toluenesulphonyl derivatives of adenosine and cytidine yield *cyclo*nucleoside salts when heated in acetone solution. Since the cyclisation can only occur with a β-glycoside, and involves only interaction between the 5′-position in the sugar residue and $N_{(3)}$ in adenosine, or the oxygen attached to $C_{(2)}$ in cytidine, it seemed reasonable to expect that this method would apply equally to deoxyadenosine (I; R = R′ = H) and deoxycytidine (III; R = H) provided that the sugar residue in these compounds is attached respectively to $N_{(9)}$ in the purine and $N_{(3)}$ in the pyrimidine nucleus.

As a first step in seeking to apply this method to deoxyadenosine it was necessary to prepare a 3′-substituted deoxyadenosine so that a toluene-*p*-sulphonyl group could be introduced unambiguously into position 5′. This was not altogether easy, since the manipulation of deoxyadenosine derivatives is complicated by the extreme lability of the glycosidic linkage. Treatment of deoxyadenosine with slightly more than 1 molar proportion of triphenylmethyl chloride in pyridine yielded a monotrityl derivative which we formulate as 2′-deoxy-5′-trityladenosine, substitution of the primary hydroxyl group under such conditions being a general phenomenon in carbohydrate derivatives. Acetylation of this product gave *N* : 3′-diacetyl-2′-deoxy-5′-trityladenosine which could not be crystallised. Attempts to remove the trityl group with acetic acid of varying strengths, or with ammonium chloride in ethanol, failed, the glycosidic linkage being largely hydrolysed. Hydrogenation in ethanol in presence of a mixture of palladium and palladised charcoal proved the only practicable method. This was far from satisfactory; not only was it extremely slow and incomplete, but the labile *N*-acetyl group was largely removed and extensive fission of the glycosidic linkage also occurred. In this way a small amount of the crystalline 3′-acetyl-2′-deoxyadenosine was obtained, sufficient for purposes of identification, but it was clear that the route to it was useless for preparative purposes. Recourse was therefore had to partial acetylation of deoxyadenosine. The nucleoside was allowed to react with acetic anhydride in pyridine at room temperature for three hours, and the product subjected to countercurrent distribution with an ethyl acetate–water system in an automatically operated 100-stage apparatus. In this way three acetylated nucleosides were



isolated in addition to unchanged deoxyadenosine. The major product, a diacetyldeoxyadenosine, accounted for some 55% of the acetylated material, while the remainder was made up of two monoacetyldeoxyadosines (32% and 13%). The monoacetyl compound obtained in smaller amount was identical with 3′-acetyl-2′-deoxyadenosine prepared *via* the 5′-trityl derivative. This being so it is reasonable to conclude that the other monoacetate was 5′-acetyl-2′-deoxyadenosine and the diacetate 3′ : 5′-diacetyl-2′-deoxyadenosine.

Toluene-*p*-sulphonylation of 3′-acetyl-2′-deoxyadenosine gave a resinous 3′-acetyl-2′-

deoxy-5′-toluene-*p*-sulphonyladenosine (I; R = $C_7H_7{\cdot}SO_2$, R′ = Ac) which was insoluble in water and readily soluble in organic solvents. When this product was heated in acetone a colourless crystalline compound separated, which analysed correctly for a toluene-*p*-sulphonyl derivative of 3′-acetyl-2′-deoxyadenosine but had the properties of a salt. It was freely soluble in water and insoluble in chloroform, and on paper chromatography it gave two spots, one showing ultra-violet absorption (purine) and the other having an acidic reaction (toluene-*p*-sulphonic acid); moreover, determination of molecular weight by the cryoscopic method gave values approximately half that expected for the covalent toluene-*p*-sulphonate. These properties correspond closely to those of the *cyclo*nucleoside salt obtained in similar fashion from 2′ : 3′-*iso*propylidene-5′-toluene-*p*-sulphonyladenosine (Clark, Todd, and Zussman, *loc. cit.*) and we therefore formulate our product as 3′-acetyl-2-′deoxy-3 : 5′-*cyclo*adenosine toluene-*p*-sulphonate (II). As in the case of the corresponding adenosine derivatives, cyclisation caused a marked shift of the ultra-violet absorption maximum to longer wave-length.

The formation of a *cyclo*nucleoside salt in this way indicates that deoxyadenosine (I) is a 2′-deoxy-β-D-ribofuranoside since examination of molecular models shows that only in the β-configuration is a cyclisation of this nature possible. Toluene-*p*-sulphonylation of 5′-acetyl-2′-deoxyadenosine gave a crystalline covalent 5′-acetyl-2′-deoxy-3′-toluene-*p*-sulphonyladenosine which could not be converted into an ionic isomer. This fact adds further confirmation to our formulation of the isomeric monoacetyl derivatives of deoxyadenosine.

Attention was now turned to deoxycytidine (III; R = H). Toluene-*p*-sulphonylation of *N* : 3′-diacetyl-2′-deoxycytidine (Michelson and Todd, *J.*, 1954, **34**) gave a resinous substance converted by treatment with methanolic ammonia into crystalline 2′-deoxy-5′-toluene-*p*-sulphonylcytidine (III; R = $C_7H_7{\cdot}SO_2$). Deacetylation was carried out in this instance since, the formation of *cyclo*nucleoside salts depending on the basic nature of the purine or pyrimidine residue in the nucleoside, *N*-acylation of the cytosine residue might well prevent its occurrence. When an acetone solution of 2′-deoxy-5′-toluene-*p*-sulphonylcytidine was heated a gum was precipitated which, however, was not completely soluble in water. Examination by paper chromatography indicated that it was a mixture in which cytosine and toluene-*p*-sulphonate ion, as well as sugar derivatives of unidentified nature, were present. An attempt to cyclise *N* : 3′-diacetyl-2′-deoxy-5′-toluene-*p*-sulphonylcytidine gave mainly unchanged starting material, the remainder being converted into a similar mixture of decomposition products. Despite the failure of all efforts to isolate the expected 2′-deoxy-O^2 : 5′-*cyclo*cytidine *p*-toluenesulphonate (IV) after heating of 2′-deoxy-5′-toluene-*p*-sulphonylcytidine, the observation that toluene-*p*-sulphonate ion is present in the product makes it almost certain that the *cyclo*nucleoside is indeed formed by this process. We are at present unable to give a full explanation for its evident very ready decomposition. It may be recalled, however, that 2′ : 3′-*iso*propylidene-O^2 : 5′-*cyclo*cytidine toluene-*p*-sulphonate is not very stable; it is hydrolysed readily with acid, yielding cytidine, and decomposes partially on paper chromatography in presence of bases (Clark, Todd, and Zussman, *loc. cit.*). It would be expected that the deoxy*cyclo*cytidine would be even less stable since, as pointed out by Dr. V. M. Clark, the presence of a positive charge on $N_{(3)}$ in such a deoxyriboside derivative would lead to instability of the $N_{(3)}$–$C_{(1')}$ as well as of the O^2–$C_{(5')}$ linkage. Elimination of the sugar residue and production of cytosine might thus be expected, and indeed was observed in our experiments. We therefore consider that our results support the conclusion that 2′-deoxy-5′-toluene-*p*-sulphonylcytidine does undergo conversion into an unstable *cyclo*nucleoside salt, and that deoxycytidine (III; R = H) is accordingly to be regarded as a 2′-deoxy-β-D-ribofuranoside.

In the ribonucleoside series, determination of the β-configuration at the glycosidic centre in adenosine and cytidine suffices to prove the β-configuration for all four natural nucleosides, since guanosine and adenosine can be synthesised from a common precursor and cytidine can be converted into uridine. No such interrelationship exists between deoxyadenosine and deoxycytidine on the one hand and the remaining deoxyribonucleosides (deoxyguanosine, thymidine, 5-methyldeoxycytidine) and so, strictly, each individual should be examined separately. Nevertheless, it seems virtually certain that if deoxy-

adenosine and deoxycytidine are β-glycosides then all the natural deoxyribonucleosides are β-glycosides. This follows from *X*-ray studies carried out on deoxyribonucleic acid; the regularities observed in the packing of nucleoside residues in the macromolecule demand that the individual nucleosides must all have the same configuration (α or β) at the glycosidic centre (cf. Astbury, *Symp. Soc. Exp. Biol.*, 1947, **1**, 66).

Experimental

2′-Deoxy-5′-trityladenosine.—Anhydrous deoxyadenosine (prepared by drying 10·9 g. of the monohydrate overnight at 100°/0·1 mm.) was dissolved in warm dry pyridine (300 c.c.). The solution was cooled to room temperature, and triphenylmethyl chloride (12·45 g., 1·1 mol.) was added and dissolved by shaking. The mixture was set aside for 1 week, then poured into ice-cold aqueous sodium carbonate (8 g. in 1200 c.c.). The whole was evaporated to dryness under reduced pressure, the residue shaken with acetone (500 c.c.) at 35°, and the acetone solution filtered and evaporated *in vacuo*, giving a solid foam which readily disintegrated to a fine powder. The powder was shaken for 2 hr. at room temperature with benzene (250 c.c.), the mixture filtered, and the residue washed with benzene and air-dried; it consisted of a mixture of the required trityl derivative and unchanged deoxyadenosine. The latter (3·2 g.) was removed by stirring with water (200 c.c.) at 60° and the residual powder (11·5 g.) was dried and recrystallised by dissolving it in hot acetone (250 c.c.) and adding light petroleum (500 c.c.; b. p. 60—80°), giving *2′-deoxy-5′-trityladenosine* (8·86 g.), m. p. 195—197° (Found: C, 70·8; H, 5·8; N, 14·4. $C_{29}H_{27}O_3N_5$ requires C, 70·6; H, 5·5; N, 14·2%). The yield of trityl compound was 62% after allowance for recovered starting material.

N : *3′-Diacetyl-2′-deoxy-5′-trityladenosine.*—2′-Deoxy-5′-trityladenosine (2 g.) was dissolved in dry pyridine (50 c.c.), acetic anhydride (20 c.c.) was added, and the mixture kept overnight at room temperature. The solution was poured into ice-water (600 c.c.) and left overnight and the precipitate (2·3 g.) was collected, dried, and then freed from pyridine by evaporation with benzene (500 c.c.). The residue was dissolved in ethanol, and the solution filtered and evaporated. N : *3′-Diacetyl-2′-deoxy-5′-trityladenosine* was thus obtained as a solid foam which did not crystallise (Found: C, 68·4; H, 5·5; N, 12·2. $C_{33}H_{31}O_5N_5$ requires C, 68·6; H, 5·4; N, 12·1%).

3′-Acetyl-2′-deoxyadenosine.—(a) *From* N : *3′-diacetyl-2′-deoxy-5′-trityladenosine.* The above diacetyl trityl compound (3·4 g.) was hydrogenated in ethanol (150 c.c.) at 40—50° in presence of palladised charcoal (0·5 g. of 10%) and palladium oxide (1·7 g.). Uptake of hydrogen was exceedingly slow and even after several days only about half of the theoretical amount had been absorbed. Despite numerous trials under various conditions we were unable to improve this procedure and the time of hydrogenation varied from 3 to 10 days. The solution was filtered and evaporated, and the residue shaken with light petroleum (100 c.c., b. p. 40—60°) at room temperature overnight. The insoluble portion was then dissolved in hot ethanol (30 c.c.). On cooling, a small white precipitate separated and was filtered off; paper chromatography showed that it was mainly adenine. The filtrate was concentrated to smaller bulk (15 c.c.) and set aside. Colourless crystals (170 mg.) separated and were collected; examined by paper chromatography they appeared to consist largely of one compound (R_F 0·50—0·55 in *n*-butanol–water; 0·50 with 5% aqueous disodium hydrogen phosphate) mixed with adenine. Examination of the mother-liquors showed that they contained more adenine but little of the other substance. The crystalline material was twice recrystallised from ethanol and then gave colourless prisms of *3′-acetyl-2′-deoxyadenosine* (61 mg.), m. p. 211—212·5° (Found: C, 49·0; H, 5·3; N, 24·1. $C_{12}H_{15}O_4N_5$ requires C, 49·1; H, 5·2; N, 23·9%).

(b) *By partial acetylation of deoxyadenosine.* Anhydrous deoxyadenosine (8·7 g.; dried for 12 hr. at 80°/0·5 mm.) was dissolved in dry pyridine (310 c.c.). Acetic anhydride (18·1 c.c., 6 mols.) in dry pyridine (310 c.c.) was added, the mixture left for 3 hr. at room temperature and then poured into ice-water (100 c.c.), and the whole was evaporated under reduced pressure (bath-temp. $< 40°$), a process which ensured removal of *N*-acyl groups. The residual resin was twice evaporated with ethanol (50 c.c.), then dissolved in water previously saturated with ethyl acetate (41 c.c.). This solution was placed in the first two stages of an automatically operated 100-stage countercurrent distribution apparatus. With ethyl acetate–water the distribution process was continued until one hundred withdrawal stages had been completed. Determination of the optical density at 260 mμ in each of the hundred fractions removed from the apparatus after completion of the distribution showed three distinct peaks; on this basis the following groups were bulked: fractions 3—16, 18—56, and 58—83. The 100 withdrawal stages were similarly bulked.

Fractions 3—16 on evaporation yielded deoxyadenosine (0·7 g.). Fractions 58—83 on evaporation gave 3′-acetyl-2′-deoxyadenosine (0·9 g.), hexagonal prisms from ethyl acetate (Found: C, 49·3; H, 5·5; N, 23·9%). The m. p. of the purified 3′-acetyl derivative [216—217° (softens 214—216°)] was slightly higher than that of the material prepared as above *via* the trityl compound, but was not depressed when the two were mixed, and both materials showed the same behaviour on paper chromatograms and had identical infra-red spectra. Light absorption in ethanol: max. at 260 mμ (ε 14,300).

5′-Acetyl-2′-deoxyadenosine. The bulked fractions 18—56 from the above countercurrent distribution experiment were evaporated and the residue recrystallised from ethanol. *5′-Acetyl-2′-deoxyadenosine* (2·3 g.) was thus obtained as colourless needles, m. p. 140—141° (Found: C, 49·5; H, 5·3; N, 23·9%). Light absorption in ethanol: max. at 260 mμ (ε 14,400).

3′ : 5′-Diacetyl-2′-deoxyadenosine.—The combined withdrawal stages from the above countercurrent distribution were evaporated and the residue recrystallised from ethyl acetate–light petroleum (b. p. 40—60°). *3′ : 5′-Diacetyl-2′-deoxyadenosine* (4·0 g.) formed needles, m. p. 151—152° (Found, in material dried at 120°/10^{-3} mm. for 15 hr.: C, 50·3; H, 4·9; N, 20·4. $C_{14}H_{17}O_5N_5$ requires C, 50·2; H, 5·1; N, 20·9%). Light absorption in ethanol: max. at 259 mμ (ε 14,800).

3′-Acetyl-2′-deoxy-5′-toluene-p-*sulphonyladenosine.*—3′-Acetyl-2′-deoxyadenosine (240 mg.; dried for 12 hr. at 100°/0·1 mm.) was dissolved in dry pyridine (25 c.c.) and cooled in ice. Toluene-*p*-sulphonyl chloride (235 mg., 1·3 mols.) was added and the solution was set aside overnight at room temperature. Ice-cold saturated aqueous sodium hydrogen carbonate (10 c.c.) was added and the mixture was extracted with ice-cold chloroform. Evaporation of the dried chloroform extract gave a resin which was redissolved in chloroform, then filtered, and light petroleum (b. p. 60—80°) was added to opalescence. After 12 hr. unchanged 3′-acetyl-2′-deoxyadenosine (40 mg.) separated and was filtered off. The filtrate was further diluted with light petroleum (1·5 vols.) and left overnight. The resin which separated was washed with light petroleum and converted into a solid foam (250 mg.) by removal of traces of solvent under reduced pressure (0·01 mm.). This material, which did not crystallise, was essentially the required toluene-*p*-sulphonyl derivative, although paper chromatography in *n*-butanol–water showed that it contained small amounts of deoxyadenosine and 3′-acetyl-2′-deoxyadenosine (Found: C, 50·2; H, 4·7; N, 14·6. Calc. for $C_{19}H_{21}O_6N_5S$: C, 51·0; H, 4·7; N, 15·7). Light absorption in ethanol: max. at 257 mμ.

*3′-Acetyl-2′-deoxy-3 : 5′-cyclo**adenosine** Toluene*-p-*sulphonate.*—3′-Acetyl-2′-deoxy-5′-toluene-*p*-sulphonyladenosine (240 mg.) was heated in dry acetone (10 c.c.) in a sealed tube at 100° during 1¼ hr. Colourless crystals (70 mg.) of the cyclo*nucleoside* salt, m. p. 195·5°, separated. A further quantity was obtained by evaporation of the mother-liquors, dissolution of the residue in dioxan (10 c.c.), and refluxing for 2 hr.; the salt (90 mg.) which separated again had m. p. 195·5° [Found: C, 50·8; N, 4·6; N, 15·8%; *M* (Rast), 262, 244. $C_{19}H_{21}O_6N_5S$ requires C, 51·0; H, 4·7; N, 15·7%; *M*, 447] (total yield of crystalline salt was 67%). It was extremely soluble in water and insoluble in boiling chloroform, acetone, or dioxan. Light absorption in ethanol: max. at 274—275 mμ (ε 14,900).

Comparison of Covalent and Ionic Toluene-p-*sulphonates from 3′-Acetyl-2′-deoxyadenosine.*—The covalent isomer ran as a single spot on paper chromatography whereas the ionic compound gave a purine spot detectable by ultra-violet absorption and an acidic spot detectable by spraying with B.D.H. Universal Indicator, starch–iodide–iodate, or bromophenol-blue. Paper chromatographic comparisons are summarised below in Table 1.

5′-Acetyl-2′-deoxy-3′-toluene-p-*sulphonyladenosine.*—To an ice-cold solution of 5′-acetyl-2′-deoxyadenosine (255 mg.; dried for 12 hr. at 80°/0·1 mm.) in dry pyridine (3 c.c.) toluene-*p*-sulphonyl chloride (180 mg., 1·1 mols.) was added; the resulting orange solution was set aside overnight at room temperature. Ice-cold saturated aqueous sodium hydrogen carbonate (10 c.c.) was added, the mixture extracted with ice-cold chloroform, and the extract dried and evaporated. The yellowish solid residue (330 mg.) was recrystallised from chlorofrom–light petroleum (b. p. 60—80°), giving *5′-acetyl-2′-deoxy-3′-toluene*-p-*sulphonyladenosine* as plates (100 mg.), m. p. 147—148° (Found: C, 51·1; H, 4·8; N, 15·6. $C_{19}H_{21}O_6N_5S$ requires C, 51·0; H, 4·7; N, 15·7%). The compound was quite unaffected by refluxing it in dry dioxan or by heating its acetone solution in a sealed tube at 100°.

2′-Deoxy-5′-toluene-p-*sulphonylcytidine.*—Toluene-*p*-sulphonyl chloride (60 mg.) was added to a solution of *N* : 3′-diacetyl-2′-deoxycytidine (75 mg.; Michelson and Todd, *J.*, 1954, 34) in dry pyridine (2 c.c.), and the mixture left at room temperature for 20 hr., then cooled to 0°. Water (0·2 c.c.) was added, and after 1 hr. at 0° the mixture was poured into ice-water (25 c.c.)

and extracted with chloroform. The chloroform extract was washed successively with ice-cold dilute sulphuric acid, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated under reduced pressure. The crude *N* : 3′-diacetyl-2′-deoxy-5′-toluene-*p*-sulphonylcytidine (85 mg.) thus obtained as a solid foam was not further purified. A quantity of it (75 mg.) was dissolved in cold half-saturated methanolic ammonia (2 c.c.) and after 20 hr. at 0° the mixture was evaporated under reduced pressure. A small amount of water was added to the

TABLE 1. *Paper chromatography of deoxyadenosine derivatives.*

Whatman No. 1 paper. Ascending R_P values.
Solvent systems: I, *n*-butanol–water (86 : 14); II, *tert.*-butanol–acetic acid–water (5 : 4 : 1); III, ethanol–ammonia–water (80 : 16 : 4); IV, 5% aqueous disodium phosphate–*iso*amyl alcohol (3 : 2).

	I	II	III	IV
Deoxyadenosine	0·40	0·75	0·47	0·55
3′ : 5′-Diacetyl-2′-deoxyadenosine	0·66	0·90	0·59	0·62
5′-Acetyl-2′-deoxyadenosine	0·56	0·82	0·51	0·62
3′-Acetyl-2′-deoxyadenosine	0·58	0·83	0·53	0·52
5′-Acetyl-2′-deoxy-3′-toluene-*p*-sulphonyladenosine	0·86	0·91	0·70	Streak at origin
3′-Acetyl-2′-deoxy-5′-toluene-*p*-sulphonyladenosine	0·82	0·84	0·67	Streak at origin
3′-Acetyl-2′-deoxy-3 : 5′-*cyclo*adenosine toluene-*p*-sulphonate :				
purine moiety	—	0·62	0·49	0·79
toluene-*p*-sulphonate ion	—	0·49	0·67	—

residue, and the crystalline deposit of 2′-*deoxy*-5′-*toluene*-p-*sulphonylcytidine* (50 mg.) was collected. Recrystallised from water it had m. p. 120° (Found, in material dried for 12 hr. at 90°/0·1 mm.: C, 50·5; H, 5·0. $C_{16}H_{19}O_6N_3S$ requires C, 50·4; H, 5·0%).

Action of Heat on 2′-*Deoxy*-5′-*toluene*-p-*sulphonylcytidine and* N : 3′-*Diacetyl*-2′-*deoxy*-5′-*toluene*-p-*sulphonylcytidine.*—A solution of 2′-deoxy-5′-toluene-*p*-sulphonylcytidine (40 mg.) in acetone (3 c.c.) was heated in a sealed tube at 100° for 2 hr., during which a gum slowly separated. Acetone was removed and the residue, which was only in part soluble in water, was examined by paper chromatography. Several spots were observed, indicating extensive decomposition of the *cyclo*nucleoside salt. Application of the same heating process to crude *N* : 3′-diacetyl-2′-deoxy-5′-toluene-*p*-sulphonylcytidine gave similar results; the product was for the most part insoluble in water and it contained a large amount of unchanged material. The results of these studies are given in Table 2, ascending R_F values of appropriate known substances as well as starting materials being recorded for comparison.

TABLE 2. *Paper chromatography of deoxycytidine derivatives.*

Whatman No. 1 paper. Ascending R_F values.
Solvent systems: I—III, see Table 1; IV, *iso*propanol–water–ammonia (7 : 2 : 1).

	I	II	III	IV
Cytosine	0·13	0·54	0·46	0·47
Acetylcytosine	0·28	0·73	0·52	0·53
Deoxycytidine	0·12	0·61	0·55	0·58
N : 3′-Diacetyl-2′-deoxycytidine	0·57	0·93	0·66	0·80
N : 3′-Diacetyl-2′-deoxy-5′-toluene-*p*-sulphonylcytidine	0·76	0·95	0·80	0·88
2′-Deoxy-5′-toluene-*p*-sulphonylcytidine	0·53	0·90	0·78	0·85
Toluene-*p*-sulphonate ion	0·27	0·50	0·75	0·75
Rearranged 2′-deoxy-5′-toluene-*p*-sulphonylcytidine	0·53	0·91	0·79	0·85
	0·28	0·83	0·72	0·68
Ultra-violet absorbing spots	0·13	0·47	0·55	0·47
	0·08	0·63	0·46	0·38 and 0·28
		Fluorescent		Fluorescent
Acid spots	—	0·50	0·78	—
Basic spots	—	0·83	—	—
Cysteine spray	—	—	—	streak 0·3 to 1·0

Grateful acknowledgment is made to the Royal Commissioners for the Exhibition of 1851 for an Overseas Scholarship (to D. H. H.), to the Teknisk Videnskabelige Forskningsraad (Denmark) for a Fellowship (to W. A.) and to the Rockefeller Foundation and the American Cyanamid Company for grants.

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Aromatic Azo-compounds. Part V. The Absorption Spectra of N-Substituted 4-Aminoazobenzenes and their Mono-acid Salts.*

By G. M. Badger, R. G. Buttery, and G. E. Lewis.

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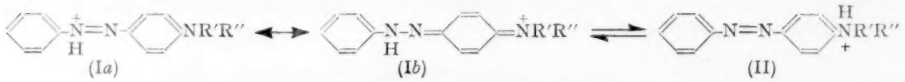
The absorption spectra of 4-aminoazobenzenes and of some *N*-substituted derivatives have been studied in neutral and in acid solutions. In general, the mono-acid salts show two absorption bands, one in the region 5000—5400 Å (*Q* band) and the other at 3200 Å (*K'* band). The results support the view that the salt cations exist in solution as an equilibrium mixture of two tautomeric forms, in which the proton is attached to the azo-linkage and to the amino-group respectively. The ionisation constants of these aminoazobenzenes have also been determined from the spectra.

4-Dimethylaminoazobenzene ("Butter Yellow") is of considerable interest in carcinogenesis as it produces a high percentage of liver tumours in rats (for reviews see Badger and Lewis, *Brit. J. Cancer*, 1952, **6**, 270; Miller and Miller, "*Adv. Cancer Res.*," 1953, **1**, 339). Many related compounds are also carcinogenic, and it has been suggested that their activity is associated with an optimum degree of electron density at the azo-linkage (Pullman, *Compt. rend.*, 1946, **222**, 1501; 1947, **224**, 1773; Pullman and Pullman, *Rev. Sci.*, 1946, **84**, 145). In order to study this hypothesis experimentally the rates of peracid oxidation of substituted azobenzenes were determined (Badger and Lewis, *J.*, 1953, 2147). The effects of the various substituents were additive, and there was a strong correlation between the observed effect on the rate of oxidation and the magnitude of the Hammett σ constant for that substituent. Moreover, although further work was clearly required, the results were not inconsistent with the Pullman hypothesis.

Unfortunately, the reactivity of the amino-group itself towards peracids prevents the use of this technique with aminoazobenzenes (which are the most interesting derivatives in carcinogenesis). The present studies attempt to elucidate the relative effects of amino- and of substituted amino-groups on the azo-linkage.



(*Ia*) (*Ib*) (II)

It has long been maintained that hydrogen ions add to aminoazo-compounds at the azo-linkage (*Ia*) and that the observed deepening in colour is due to the contributing resonance structure (*Ib*) (Hantzsch and Hilscher, *Ber.*, 1908, **41**, 1171; Hantzsch, *ibid.*, 1919, **52**, 509; Kehrmann, *ibid.*, 1915, **48**, 1933; Bury, *J. Amer. Chem. Soc.*, 1935, **57**, 2115; Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273). In the absence of complicating factors, therefore, it was expected that the primary ionisation constants of a series of amino-azo-compounds would be an accurate measure of the relative electron densities at the azo-linkage. Rogers, Campbell, and Maatman (*J. Amer. Chem. Soc.*, 1951, **73**, 5122) have already found that there is a linear relationship between the Hammett σ constants and both the primary and secondary ionisation constants of 4'-substituted 4-dimethylamino-azobenzenes.

Following these authors' method we have evaluated the primary ionisation constants of 4-aminoazobenzene, and of various *N*-substituted derivatives, by examination of their absorption spectra in the region 3500—5000 Å at various acidities. The solvent employed was 50% (v/v) aqueous ethanol, and the optical-density measurements used in the calculations were taken in the 3800—4300-Å region. The results are given in Table 1, together with the sulphuric acid concentration necessary to convert the free base into the mono-acid salt.

Except for the methylamino- and dimethylamino-derivatives, the results are in qualitative agreement with electronic theory. The lower ionisation constants produced

* Part IV, *J.*, 1953, 2156.

by *N*-methyl-substitution, however, seem to be inconsistent with the high basicity of dimethylaniline compared with aniline (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472). This inconsistency raised doubts as to the validity of this method for determining relative electron densities at the azo-linkage. In this connection Hantzsch and Burawoy

TABLE 1. *Ionisation constants of* N-*substituted* **4**-*aminoazobenzenes.*

N-Substituent(s)	pK_a	Required acidity, N	*N*-Substituent(s)	pK_a	Required acidity, N
Ph	0·48 ± 0·03	6·8	H	2·30 ± 0·02	1·7
Me, CH_2Ph	1·64 ± 0·04	5·0	Et	2·45 ± 0·02	1·7
Me, CH_2·CH_2·OH	2·01 ± 0·03	3·1	Me, Et	2·48 ± 0·03	1·7
2Me	2·21 ± 0·02	1·7	2Et	3·05 ± 0·03	0·85
Me	2·23 ± 0·03	1·7			

(*Ber.*, 1930, **63**, 1760) suggested that the salt cations exist in solution as an equilibrium mixture of the tautomeric forms (I) and (II) in which the proton is attached to the azo-linkage and to the amino-group, respectively. Spectrographic data were cited to support this suggestion, but as further information seemed desirable the present studies were extended to cover the range 2200—6600 Å in both neutral and acid solution. The results are collected in Table 2.

TABLE 2. *Wave-lengths* (Å) *of the maxima and corresponding intensities* ($\times 10^{-3}$) *in parentheses in the absorption spectra of azobenzenes and their mono-acid salts in aqueous ethanol.*

Compound	Free base	Mono-acid salt	
	K band	*K′* band	*Q* band
Azobenzene	3200 (21·1)	—	—
Azoanisole	3500 (16)	—	5000 (43)
4-Phenylaminoazobenzene	4200 (28)	—	5400 (61)
4-(*N*-Methylbenzylamino)azobenzene	4200 (27)	3200 (9)	5300 (41)
4-(*N*-Methyl-2-hydroxyethylamino)azobenzene	4200 (26)	3200 (7)	5200 (47)
4-Dimethylaminoazobenzene	4200 (24)	3200 (10)	5200 (34)
4-Methylaminoazobenzene	4100 (23)	3200 (8)	5100 (39)
4-Aminoazobenzene	3800 (22)	3200 (18)	5000 (11)
4-Ethylaminoazobenzene	4100 (24)	3200 (13)	5100 (29)
4-(*N*-Ethylmethylamino)azobenzene	4300 (25)	3200 (15)	5300 (22)
4-Diethylaminoazobenzene	4400 (29)	3200 (20)	5200 (10)

Azobenzene has a strong absorption band (*K* band) at 3200 Å in neutral solution, and the spectra of aminoazobenzenes were found to be similar except that the *K* band is displaced bathochromically by about 600—1200 Å. On acidification, the *K* band was replaced by a band in the 5000—5400 Å region (*Q* band) and another at the constant wave-length of 3200 Å (*K′* band).

As Rogers, Campbell, and Maatman (*loc. cit.*) have shown, addition of the proton to the amino-group should result in the spectrum of the mono-acid salt being similar to that of azobenzene. 4-Dimethylaminoazobenzene methiodide has virtually the same absorption spectrum as azobenzene (Hantzsch and Hilscher, *loc. cit.*; Hantzsch and Burawoy, *loc. cit.*; Pongratz, Markgraf, and Mayer-Pitsch, *Ber.*, 1938, **71**, 1287). It is noteworthy that the *K′* bands of the mono-acid salts invariably occur at 3200 Å, the wave-length of the characteristic *K* band of azobenzene. In agreement with Hantzsch and Burawoy (*loc. cit.*), it seems that the *K′* band is associated with the ammonium form of the cation (II) and that the *Q* band is derived from the azonium form (I). In support of this, the mono-acid salt of 4 : 4′-azoanisole, which presumably exists only in the azonium form, shows an intense *Q* band at 5000 Å, but no peak at 3200 Å. It seems, then, that the cations are present as an equilibrium mixture in solution, the relative intensities of the *Q* and *K′* bands giving the approximate proportions of the two tautomers present.

The influence of a substituent at the amino-nitrogen atom on the position of the equilibrium will depend on its size and its electronic effect. Although electronic effects should be straightforward, and either increase or decrease the basicity, large substituents could hinder both the entrance of the hydrogen ion to the amino-nitrogen and the tendency

of the amino-group to assume coplanarity with the rest of the molecule. A comparison of the extinction coefficients of the K' and Q bands (Table 2) with the basicities (Table 1) shows that there is a general increase in the tendency for salts to exist in the ammonium form as the ionisation constants increase. The primary ionisation constants do not measure the relative electronic effects of amino- and substituted amino-groups on the azo-linkage, but merely the over-all basicity.

The published spectra of some methyl-4-dimethylaminoazobenzenes are interesting. Miller, Sapp, and Miller (*J. Amer. Chem. Soc.*, 1948, **70**, 3458) found that 4-dimethylamino-3-methylazobenzene has no absorption peak in the 5000-Å region in acid solution, but a very intense K' band at 3200 Å. This is because the 3-methyl group prevents the dimethylamino-group becoming coplanar with the ring system so that its tautomeric effect at the azo-linkage is restricted. In these circumstances the proton undoubtedly adds on to the amino-group in preference to the azo-nitrogen atom. Price and Lincoln (*J. Amer. Chem. Soc.*, 1951, **73**, 5838) attribute a much lower σ constant (−0·360) to the 4-dimethylamino-3-methyl group combination than to the 4-dimethylamino-group alone (−0·720).

Miller, Sapp, and Miller (*loc. cit.*) also showed that there is a marked difference between the spectra of 4-dimethylamino-2-methylazobenzene and that of 4-dimethylamino-2′-methylazobenzene. The former shows an intense Q band and a much weaker peak at 3200 Å; but the latter has an intense K' band at 3200 Å and a much weaker Q band. It has been shown (Badger and Lewis, *J.*, 1953, 2147; Badger and Buttery, *J.*, 1953, 2156) that *o*-methyl groups afford considerable steric hindrance at the nearer azo-nitrogen atom, and the preferential attachment of the hydrogen ion to the amino-group in 4-dimethylamino-2′-methylazobenzene, as shown by its spectrum in acid solution, is satisfactorily explained on this basis. With 4-dimethylamino-2-methylazobenzene there is no steric hindrance with the azo-nitrogen atom in question and the attack of the proton is therefore unhindered. This results in the predominant formation of the azonium cation, and hence the intense Q band observed.

Experimental

4-Aminoazobenzene.—This was prepared from diazoaminobenzene (Vogel, "Textbook of Practical Organic Chemistry," Longmans Green and Co., 1948, p. 599), and had m. p. 125°.

4-Methyl- and 4-Ethyl-aminoazobenzene.—These were prepared by the action of the appropriate alkyl halide on 4-aminoazobenzene (Berju, *Ber.*, 1884, **17**, 1401). They had m. p. 88° and 87°, respectively.

Phenylaminoazobenzene.—This was formed by coupling benzenediazonium chloride with diphenylamine (Witt, *Ber.*, 1879, **12**, 259). It had m. p. 82°.

NN-*Disubstituted Aminoazobenzenes.*—In each case these were prepared from benzenediazonium chloride and the appropriate disubstituted aniline (Miller and Miller, *J. Exptl. Med.*, 1948, **87**, 139). The melting points agreed with those recorded by Miller and Miller.

Chromatography.—All compounds were purified by passage through alumina, and finally recrystallised from benzene–light petroleum.

Solvent.—The aqueous ethanol used throughout was prepared from equal volumes of distilled water (or sulphuric acid of the requisite concentration) and absolute alcohol which had been refluxed over solid sodium hydroxide and subsequently fractionated.

pH *Measurements.*—These were made with a Cambridge bench type pH meter. In highly acidic solutions the total concentration of sulphuric acid was used as a guide to the approximate pH (Michaelis and Granick, *J. Amer. Chem. Soc.*, 1942, **64**, 1861).

Absorption Spectra.—All spectra were determined with a Hilger "Uvispek" spectrophotometer. The concentration of azo-compound in each case was $0{\cdot}5 \times 10^{-4}$M.

Ionisation Constants.—These were calculated from optical-density measurements, after Beer's law had been checked. The acidities necessary to complete the addition of the first hydrogen ion were determined by plotting optical densities against pH.

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α-1 : 4-*Glucosans. Part I. The Inter-chain Linkages in Glycogens.*

By D. J. Bell and D. J. Manners.

[Reprint Order No. 5093.]

Four glycogens and two glycogen α-dextrins, subjected to prolonged periodate oxidation (maximal formic acid production) followed by acid hydrolysis, yielded no significant amounts of glucose. It is concluded that these polysaccharides contain only α-1 : 4- and 1 : 6-linkages.

It is often assumed that *all* the inter-chain linkages in *all* glycogens are 1 : 6 (cf., *e.g.*, Myrbäck and Sillén, *Nature*, 1949, **163**, 410; *Acta Chem. Scand.*, 1949, **3**, 190; Cori and Larner, *J. Biol. Chem.*, 1951, **188**, 17), but without conclusive chemical proof apart from one isolated experiment on a single sample (Gibbons and Boissonnas, *Helv. Chim. Acta*, 1950, **33**, 1477). Previous workers have excluded the possibility of 1 : 2-linkages and have shown the presence of some 1 : 6-linkages; certain experiments, however, indicate that glycogens might contain a mixture of inter-chain 1 : 3- and 1 : 6-linkages (Carlquist, *Acta Chem. Scand.*, 1948, **2**, 770; Bell, *J.*, 1948, 992; *Angew. Chem.*, 1948, *A*, **60**, 79). This communication describes experiments which show that over 99% of the inter-chain linkages are 1 : 6 in several samples of glycogen of known biological origin. For a preliminary account see Manners, *Biochem. J.*, 1953, **55**, xx.

First attempts to characterise the inter-chain linkages in branched α-1 : 4-glucosans of the glycogen type were based on methylation studies. Hydrolysis of the trimethyl ether of a 12-unit glycogen should yield tetra-, tri-, and di-*O*-methylglucose in the molecular ratio of 1 : 10 : 1, the last sugar arising from the branch point. In practice, however, the amount of di-*O*-methylglucose always exceeds that of the tetra-*O*-methyl derivative, and the observed ratio of the methyl ethers of glucose approximates to 1 : 9 : 2 (Bell, *Biochem. J.*, 1935, **29**, 2031; 1937, **31**, 1683; *J.*, 1948, 992). Similarly, methylated 18-unit glycogens on hydrolysis give tetra-, tri-, and di-*O*-methylglucose in the ratio 1 : 15 : 2 instead of the expected ratio of 1 : 16 : 1 (Bell, *Biochem. J.*, 1936, **30**, 1612, 2144). In these experiments the observed methoxyl content of the glycogens (43·9—45·5%) indicated that etherification was not complete, despite repeated treatment with the appropriate methylating reagents (tri-*O*-methylglycogen requires OMe 45·6%; cf. Bell, *Ann. Review Biochem.*, 1949, **18**, 87). Part of the di-*O*-methylglucose therefore arose from glucose units which had not been fully etherified and not from the branch points. Furthermore small amounts of di-*O*-methylglucose can arise by demethylation of higher homologues during the acid hydrolysis of methylated glycogen (Bell, *J.*, 1948, 992). Despite these complications, for some time, methylation was the only method for identifying the inter-chain linkages of glycogen. Haworth, Hirst, and Isherwood (*J.*, 1937, 577) showed that a sample of methylated 18-unit rabbit-liver glycogen (OMe 43·3%) yielded a considerable proportion of 2 : 3-di-*O*-methylglucose, and concluded that $C_{(6)}$ was involved in the inter-chain linkages. More recently, Bell (*loc. cit.*) examined the di-*O*-methyl fraction from methylated samples of 12-unit rabbit-liver and 11-unit rabbit-muscle glycogen (OMe 44·7 and 44·2% respectively), and found 2 : 6-di-*O*-methylglucose as the major component in each case, suggesting the possible presence of a number of 1 : 3-linkages. In contrast, Hirst, Hough, and Jones (*J.*, 1949, 928) reported hydrolysis of a methylated rabbit-liver glycogen (OMe 43%) to yield tetra-*O*-methylglucose (1), tri-*O*-methylglucose (8·6), 2 : 3-di-*O*-methylglucose (1·2), 3 : 6-di-*O*-methylglucose (1·5 moles), and mono-*O*-methylglucose (0·3 mole). In general, the methylation studies failed to yield conclusive evidence on the nature of the inter-chain linkages.

An alternative method involves partial depolymerisation with dilute acid. Analysis of the hydrolysate for disaccharides other than maltose will enable the inter-chain linkage of glycogen to be identified, provided that experimental conditions do not allow acid-reversion from glucose to occur. This method has been applied to rabbit-liver glycogen by Wolfrom, Lassettre, and O'Neill (*J. Amer. Chem. Soc.*, 1951, **73**, 595); a partial acid hydrolysate, after acetylation and chromatography, yielded a small amount of β-D-*iso*-maltose octa-acetate, and its isolation was taken as evidence for inter-chain 1 : 6-linkages.

Although the yield of *iso*maltose was only 1—2% (a 13-unit glycogen theoretically should give 6·8% of *iso*maltose), none was formed by a similar acid treatment of amylose. These experiments do not, of course, exclude the presence of a small number of 1 : 2- or 1 : 3-linkages.

The method used in the present investigation was that developed by Hirst, Jones, and Roudier (*J.*, 1948, 1779) involving acid hydrolysis of the periodate-oxidised polysaccharide. Each glucose unit, except those linked through $C_{(2)}$ or $C_{(3)}$ will be oxidised, and on hydrolysis will yield a dialdehyde; the presence of glucose in the hydrolysate therefore indicates inter-chain 1 : 2- or 1 : 3-linkages, always assuming that periodate oxidation was complete. This method has been successfully applied to acorn and barley starch (Hirst, Jones, and Roudier, *loc. cit.*; MacWilliam and Percival, *J.*, 1951, 2259) and to certain protozoal polysaccharides (Forsyth, Hirst, and Oxford, *J.*, 1953, 2030; Forsyth and Hirst, *J.*, 1953, 2132). Whilst the present investigation was in progress, the results of Gibbons and Boissonnas (*loc. cit.*) appeared indicating that 97—98% of the inter-chain linkages in a sample of glycogen, of unspecified biological source, were 1 : 6. By a quantitative paper-chromatographic method, they assessed the acid hydrolysate of 6·0 mg. of periodate-oxidised glycogen to contain 0·016 mg. of glucose; *i.e.*, the ratio of the number of inter-chain linkages at $C_{(2)}$ or $C_{(3)}$ to those at $C_{(6)}$ was not greater than 1 : 42. Gibbons and Boissonnas obtained a similar result for potato amylopectin; in both instances, the small amount of glucose found by these workers was possibly due to incomplete oxidation of the interior chains in the polysaccharides since the oxidation period (by sodium metaperiodate) was only 12 days (cf. Experimental section).

Abdel-Akher, Hamilton, Montgomery, and Smith (*J. Amer. Chem. Soc.*, 1952, **74**, 4970) investigated the fine structure of polysaccharides by hydrogenation and subsequent acid hydrolysis of a periodate-oxidised polysaccharide. A sample of glycogen (biological source unspecified) thus yielded 1% of glucose. These workers suggested that the glucose arose from 1 : 3-linkages; the significance of this finding, without additional information, must remain uncertain since the possibility of incomplete oxidation of the glycogen remains.

In the present studies, highly purified glycogens of known biological source and known degree of branching have been used (see Table 1). In an attempt to ensure complete oxidation, glycogens (from cat liver, *Mytilus edulis*, *Helix pomatia*, and *Tetrahymena pyriformis*) were oxidised by saturated aqueous potassium periodate at 15—20° for 40—50 days (cf. Halsall, Hirst, and Jones, *J.*, 1947, 1399; Bell and Manners, *J.*, 1952, 3641); no iodine was liberated, indicating absence of "over-oxidation" (cf. Halsall, Hirst, and Jones, *J.*, 1947, 1427; Greville and Northcote, *J.*, 1952, 1945). Hydrolysates of the oxidised glycogens, neutralised and concentrated, were examined on paper chromatograms and manometrically with glucose oxidase in presence of azide (cf. Bell and Manners, *loc. cit.*). The hydrolysates from cat liver, *Mytilus edulis*, and *Tetrahymena pyriformis* glycogens contained no glucose; that from *Helix pomatia* contained *ca.* 0·1 mg., corresponding to less than 1% of the inter-chain linkages being situated at $C_{(2)}$ or $C_{(3)}$. This glucose may well have originated in incomplete oxidation. Control experiments with glucose showed experimental losses of *ca.* 10%.

In an attempt to facilitate oxidation of the interior chains of glycogens, samples from fœtal sheep liver and *Ascaris lumbricoides* were treated with salivary amylase before periodate oxidation. Salivary amylase hydrolyses α-1 : 4-glucosidic linkages in both the exterior and the interior chains of glycogen, but has no action on the inter-chain linkages (cf. Whelan and Roberts, *Nature*, 1952, **170**, 748). After oxidation of these dextrins no glucose could be detected, by paper chromatography, in their hydrolysates.

The present series of experiments thus shows that glycogens from vertebrate, invertebrate, and protozoan tissues consist of unit-chains of α-1 : 4-linked glucose units which are interlinked solely by 1 : 6-glucosidic linkages. It must be noted that the configuration of the inter-chain linkage is not revealed by these experiments. The results of Wolfrom *et al.* (*loc. cit.*) and Cori and Larner (*loc. cit.*), from chemical and enzymic studies respectively, suggest that the 1 : 6-linkages have an α-configuration. None of the glycogens examined in our study contained fructose (unpublished results; cf. Peat, Roberts, and Whelan, *Biochem. J.*, 1952, **51**, xvii).

Experimental

Periodate Oxidation of Glycogens.—Glycogens [cat liver (434 mg.), *Helix pomatia* (450 mg.), *Mytilus edulis* (78 mg.), and *Tetrahymena pyriformis* (106 mg.)] were each oxidised by saturated solutions of potassium periodate (80 ml.) at room temperature and in diffuse daylight for 40—50 days. A pilot experiment (unreported) with rabbit-liver glycogen had shown that under these conditions, the oxidation of interior chains was incomplete after 18 days. Ethylene glycol (5 ml.) was added, solid was filtered off, and the filtrate was dialysed until free from iodate. 2N-Sulphuric acid (33 ml.) was added to the dialysed solutions (~100 ml.) and the mixture was kept at 95° for 8 hr. After careful neutralisation with hot aqueous barium hydroxide, and removal of barium sulphate by centrifugation, the hydrolysate (pH 5) was concentrated at 45° to *ca.* 2 ml. Samples (0·02 ml.) were examined on paper chromatograms (Hough, Jones, and Wadman, *J.*, 1950, 1702); the results are recorded in Table 1. The remainder of the concentrates were transferred to the main compartment of Warburg manometer cups, together with 0·1M-phosphate buffer (pH 7, 1·1 ml.) and 0·1M-sodium azide (0·1 ml.). Glucose oxidase solution (0·1 ml.) was placed in the side arm of the manometer cups. The observed oxygen uptakes are given in Table 1. Under these conditions, 1 mg. of glucose gave an oxygen uptake of 123 μl. (Bell and Manners, *loc. cit.*). Suitable examination of the enzyme digests showed that the glucose oxidase was not inhibited by the other hydrolysis products of the oxidised glycogens.

Table 1.

Analysis of acid-hydrolysate of periodate-oxidised glycogen

Source of glycogen	$10^{-6}M$ *	Chain length †	Paper chromatogram	Possible oxygen uptake (μl.) ‡	Observed oxygen uptake (μl.)
Cat liver	10·0	13	—	46	0
Mytilus edulis	—	5	—	21	0
Helix pomatia	—	7	Trace glucose	88	10
Tetrahymena pyriformis	9·8	13	—	11	0
Fœtal sheep liver	14·9	13	—	—	—
Ascaris lumbricoides ...	8·7	12	—	—	—

* Mol. wt. determined by light-scattering data (Harrap and Manners, *Nature*, 1952, **170**, 419).
† Potassium periodate oxidation assay (Bell and Manners, *loc. cit.*; Manners and Ryley, *Biochem. J.*, 1952, **52**, 480). ‡ Possible oxygen uptake, assuming 1% of the inter-chain linkages are at $C_{(2)}$ or $C_{(3)}$.

Control Experiment.—Glucose (54 mg.), dissolved in 0·5N-sulphuric acid (133 ml.), was kept at 95° for 8 hr. After neutralisation and concentration, as previously described, the concentrate was diluted to 50 ml. with distilled water. Aliquot portions (1 ml.) were treated with glucose oxidase; the oxygen consumed was 118 ± 1 μl. (89% of the expected 134 μl.).

Periodate Oxidation of Glycogen α-Dextrins.—Samples of fœtal sheep-liver glycogen (517·8 mg.) and *Ascaris lumbricoides* (750·7 mg.) were dissolved in water (25 ml.). Sodium chloride solution (0·5 ml.; 3% w/v), 0·1M-phosphate buffer (pH 7; 2·0 ml.) and diluted saliva (10 ml.) were added. After incubation at room temperature for 10 min., the enzyme was inactivated by boiling. At this stage, the solutions were achroic to iodine and had lost their opalescence, and the hydrolysis (as " maltose ") had reached 47% and 36% (Schaffer–Somogyi modified reagent 60; Bell and Manners, *loc. cit.*) with the mammalian and invertebrate glycogen respectively. To the α-dextrin solutions, 8% (w/v) sodium metaperiodate (25 ml.) was added, and the mixtures kept in the dark at room temperature for 14 days. Excess of periodate was neutralised by ethylene glycol (5 ml.), and the mixtures were then extracted with successive portions of chloroform to remove iodine liberated during oxidation of the reducing groups of the α-dextrins. Iodate was removed by Ag^+, and excess of Ag^+ by hydrogen sulphide. The solutions were concentrated to 50 ml. and then hydrolysed (0·5N-sulphuric acid) as previously described. The neutralised concentrate of each α-dextrin hydrolysate was examined on a paper chromatogram; neither hydrolysate contained any reducing sugars. A control experiment, with 10 mg. of glucose and 2·0 g. of potassium iodate in water (50 ml.), when examined on a chromatogram, gave an intense brown spot at the same R_G as authentic glucose.

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1 : 9-*Pyrazoloanthrone. Part III.* The Chemistry of the Two N-Methyl Derivatives of* 1 : 9-*Pyrazoloanthrone.*

By William Bradley and Clive S. Bruce.

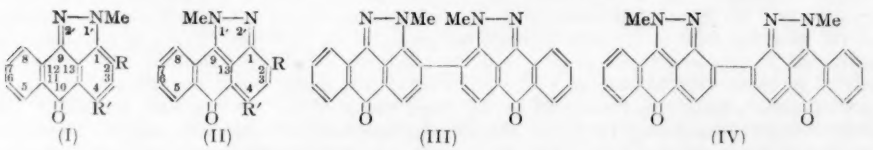
[Reprint Order No. 5121.]

The properties of the two *N*-methyl derivatives of 1 : 9-pyrazoloanthrone have been studied in continuation of previous work (*J.*, 1952, 1636). 1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (I) resembles *meso*-benzanthrone in that electron-donating agents cause nuclear substitution with or without self-union of (I). With the same reagents 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (II) undergoes self-union almost exclusively. Several derivatives of (I) and (II) are described.

Bradley and Geddes (*J.*, 1952, 1636) showed that the two *N*-methyl derivatives (I, II; R = R′ = H) of 1 : 9-pyrazoloanthrone had widely different properties, and attributed the fact to the presence of an *o*-quinonoid nucleus in (II), a consequence of bond-fixation. The two isomers and their derivatives have now been further studied in order to determine the extent of the bond-fixation effect.

Bradley and Geddes showed that heating with piperidine caused replacement of the halogen in the 2-bromo-, 4-chloro-, and 5-chloro-derivatives of 1 : 9-pyrazoloanthrone, whilst 3-bromo- and 8-chloro-derivatives were inert, and further, that the 4-bromo-derivative (I; R = H, R′ = Br) gave 4-hydroxy-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)-anthrone (I; R = H, R′ = OH) on being heated with methanolic sodium methoxide. In the present experiments the 2-bromo-, 3-bromo-, 4-bromo-, 5-chloro-, and 8-chloro-derivatives (I) have been prepared and their reactions with piperidine, morpholine, aniline, and, in two cases, with sodium methoxide have been studied. Replacement of halogen occurred readily when it occupied position 2, 4, or 5, but in the 3- or 8-position it was inert. The 2-bromo-, 5-chloro-, and 8-chloro-derivatives (II) were also prepared and it was found that the halogen of the 2-bromo-derivative was easily replaced by piperidine and morpholine, and that of the 5-chloro-compound by morpholine, whilst the 8-chloro-substituent was inert. The results indicate a marked similarity in properties of corresponding halogen derivatives whether they are derived from 1 : 9-pyrazoloanthrone or either of its *N*-methyl derivatives.

The halogen derivatives of (I) were prepared from methylhydrazine and (*a*) 1 : 2-dibromoanthraquinone (for the 2-bromo-derivative), (*b*) 1 : 3-dibromoanthraquinone (for the 3-bromo-derivative), (*c*) 1 : 5-dichloroanthraquinone (for the 5-chloro-derivative), and (*d*) 1 : 8-dichloroanthraquinone (for the 8-chloro-derivative). The halogen derivatives of (II) were prepared by the methylation of the corresponding derivatives of 1 : 9-pyrazoloanthrone (Bradley and Geddes, *loc. cit.*) by methanol and sulphuric acid.



(I) (II) (III) (IV)

1 : 9-Pyrazoloanthrone and its two *N*-methyl derivatives behave differently, however, in substitution reactions involving amines and similar reagents. These reactions are accompanied by the self-union of 1 : 9-pyrazoloanthrone and its derivatives, di-[1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthron-2-yl] (III) being formed from (I), and di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl] (IV) from (II).

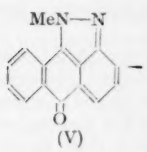
On being heated with piperidine in the presence of sodamide (I; R = R′ = H) gave (III) as the main product, 1′-methyl-2-piperidinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (I; R = NC_5H_{10}, R′ = H) being formed in small yield. Similarly with morpholine–sodamide the main product was (III), the 2-morpholino-compound (I; R = NC_4H_8O,

* Part II, *J.*, 1952, 1636.

R′ = H) resulting in small amount. The piperidino- and morpholino-derivatives were identical with the two compounds prepared by heating the corresponding 2-bromo-derivatives with piperidine and morpholine, respectively. Sodioaniline in aniline gave (III) and an anilino-derivative of (I) in approximately equal amounts. The anilino-derivative was not identical with 4- or 5-anilino-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)-anthrone. In all probability, like the morpholine and piperidine compounds, it was the 2-derivative. Methylmagnesium bromide and (I; R = R′ = H) gave 2 : 1′-dimethylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (I; R = Me, R′ = H), identical with the derivative prepared from 1-chloro-2-methylanthraquinone and methylhydrazine. Phenylmagnesium bromide gave a phenyl derivative of (I); the orientation was not established. Acetophenone and potassium hydroxide similarly converted (I; R = R′ = H) into the 2-methyl derivative (I; R = Me, R′ = H), the expected 2-phenacyl derivative (I; R = CH_2·COPh, R′ = H) being hydrolysed during the reaction. With potassium hydroxide in *tert.*-butyl alcohol the product was (III). This reaction did not occur when the medium was methyl, ethyl, or propyl alcohol; for this reason the self-union of (I) cannot involve reduction by the condensing agent. Fused potassium hydroxide caused hydroxylation and hydrolysis with opening of the ketone ring. Potassiocarbazole did not react, an indication that the nuclear reactivity of (I) towards this reagent is smaller than that of nitrobenzene (G. and M. de Montmollin, *Helv. Chim. Acta*, 1923, **6**, 94).

With piperidine and sodamide (II; R = R′ = H) gave (IV), together with a small amount of 1′-methyl-2-piperidino-pyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (II; R = NC_5H_{10}, R′ = H). Morpholine–sodamide similarly gave (IV) with a small amount of 1′-methyl-2-morpholinopyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (I; R = NC_4H_8O, R′ = H). The piperidino- and morpholino-compounds were identical with those prepared by heating the corresponding 2-bromo-derivative (II; R = Br, R′ = H) with piperidine and morpholine, respectively. Sodioaniline, methylmagnesium bromide, phenylmagnesium bromide, potassium hydroxide–acetophenone, -acetone, -acetonitrile, fused potassium hydroxide, potassium hydroxide in a range of boiling alcohols, and sodium methoxide in methanol all gave (IV) as the only product.

1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone resembles *meso*benzanthrone closely. Of the two, the latter is the more reactive as its conversion into 4 : 4′-di*meso*benzanthronyl by ethanolic potassium hydroxide at 110—120° shows. In agreement methylmagnesium iodide gives the 6-methyl derivative with *meso*benzanthrone and the 2-methyl derivative with 1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone, the substituent entering the nucleus nearer the carbonyl group in the more reactive compound (Bradley and Sutcliffe, *J.*, 1954, 708). As was stated by Bradley and Geddes (*loc. cit.*), (II; R = R′ = H) is more reactive than (I). Bases of widely different types, including the Grignard reagent, cause the self-union of (II) to (IV) unaccompanied by nuclear substitution by the reagent. The enhanced ease of self-union of (II) must be related to its *o*-quinonoid form. Yet it cannot arise simply in the marked unsaturation of *o*-quinonoid groups, for self-union is not a characteristic property of the most reactive αβ-unsaturated ketones. An alternative possibility is that the *o*-quinonoid grouping of (II) loses proton more readily than (I), the anion (V) being formed. Reaction of (V) with unchanged (II) then gives (IV) by the mechanism proposed by Bradley and Geddes.



(V)

Experimental

The 1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (I; R = R′ = H) used had m. p. 185—189° after recrystallisation from chlorobenzene, and m. p. 189° (Found: C, 77·1; H, 4·1; N, 11·9. Calc. for $C_{15}H_{10}ON_2$: C, 76·9; H, 4·2; N, 11·9%) after chromatography from benzene on alumina. 1′-Methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (II; R = R′ = H) had m. p. 229° (Found: C, 76·8; H, 4·3; N, 12·4%) after similar treatment.

Action of Reagents on (I; R = R′ = H).—(a) *Sodamide–piperidine.* Equimolar amounts of sodamide (1·9 g.) and the methyl-anthrone (11·7 g.) were refluxed in dry piperidine (50 c.c.) for 7 hr. The resulting viscous, black solution on addition to ice gave a green solution. This became reddish-brown on aeration and filtration gave a brown solid. On extraction with

concentrated hydrochloric acid the solid afforded a deep brown solution. This was filtered off, then basified with ammonia, and the precipitated tar was collected, dried, and chromatographed in benzene on alumina. The main band was reddish-brown; it was eluted with acetone, and the extract evaporated. A small amount of reddish solid, m. p. 238—240°, was obtained which did not depress the m. p. of 1′-methyl-2-piperidinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone. The material remaining from the acid extraction (5 g.) was extracted with acetone (Soxhlet). In this way di-[1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthron-2-yl] (III) was obtained as an orange-yellow solid, m. p. 355—356° (Found : C, 77·0; H, 4·3; N, 11·6. Calc. for $C_{30}H_{18}O_2N_4$: C, 77·0; H, 3·9; N, 12·0%).

(b) *Sodamide–morpholine.* When heated under reflux in dry morpholine (50 c.c.) for 6 hr., sodamide (1·9 g.) and (I; R = R′ = H) (11·7 g.) gave a blackish-green solution, which on addition to water afforded a green solution. On aeration the colour was discharged and an orange brown solid was precipitated. Treated as in (*a*), the product gave 0·5 g. of an acid-soluble substance and a much larger amount of (III), m. p. 357—358° (Found : C, 76·9; H, 4·2; N, 11·9%). The basic substance after chromatography from benzene on alumina and elution with acetone gave 1′-methyl-2-morpholinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone, m. p. 215—217°, not depressed by the authentic compound (see below).

(c) *Sodioaniline.* A solution prepared from aniline (300 c.c.), sodium (5 g.), copper bronze (0·1 g.), and nickel oxide (0·1 g.) was refluxed for 2 hr. with 8 g. of (I; R = R′ = H). Treatment as in (a) gave 6 g. of a solid. This was extracted with cold acetone, and the dissolved material was recovered, dissolved in benzene, and chromatographed on alumina. The main red-brown band was eluted with acetone, and the product, m. p. 180—181°, was further purified by sublimation *in vacuo*. *2-Anilino-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone* was obtained as bright orange crystals, m. p. 186° (Found : C, 77·65; H, 4·6; N, 12·4. $C_{21}H_{15}ON_3$ requires C, 77·45; H, 4·6; N, 12·9%) depressed to 161° on admixture with the 4-anilino-isomer. The material insoluble in cold acetone dissolved in the hot solvent. Evaporation gave (III), m. p. 354—356° (Found : C, 76·7; H, 4·0; N, 12·0. Calc. for $C_{30}H_{18}O_2N_4$: C, 77·0; H, 3·9; N, 12·0%).

(d) *Potassium hydroxide–acetophenone.* Potassium hydroxide (60 g.) and (I; R = R′ = H) (10 g.) were mixed intimately, added to dry pyridine (200 c.c.), and warmed to 50°. On the addition of acetophenone (30 c.c.) the colour became brown, then green, and after 5 hr. deep blue. After 12 hr. the resulting suspension was added to alcohol (400 c.c.) and then to ice; finally it was refluxed for 3 hr. The colour changed from blue to brown and a tar separated. This was collected when cold, and extracted with benzene, and the solution was chromatographed on alumina. Elution with benzene gave a sequence of tarry substances followed by a crystalline fraction, m. p. 210—215°. Sublimation *in vacuo* gave *1′ : 2-dimethylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone*, m. p. 216—218° (Found : C, 76·8; H, 4·9; N, 11·0. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·2%), not depressed by the authentic compound prepared from 1-chloro-2-methylanthraquinone and methylhydrazine.

Acetone also reacted with (I; R = R′ = H) in the presence of potassium hydroxide but crystalline products could not be isolated.

(e) *Methylmagnesium bromide.* 1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (5 g.) was added in small successive amounts during 30 min., and with stirring, to a solution prepared from magnesium (12 g.), methyl bromide (50 g.), and ether (500 c.c.). The resulting red solution was refluxed for 3 hr., then added gradually to acetic acid (300 c.c. of 30%). After distillation in steam a tarry product separated from the remaining solution. It was collected, dried in air, then digested with benzene. The yellowish-brown residue (4 g.; m. p. 208—212°) crystallised from chlorobenzene as bright yellow needles, m. p. 220—221° (Found : C, 77·7; H, 4·9; N, 10·7. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·2%), not depressed by authentic 1′ : 2-dimethylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone prepared by the following method :

Methylhydrazine sulphate (6 g.), 1-chloro-2-methylanthraquinone (10 g.), anhydrous potassium carbonate (10 g.), and pyridine (150 c.c.) were refluxed for 12 hr. From the cooled solution a bright yellow solid (10 g.) separated, and this crystallised from chlorobenzene as fine yellow needles, m. p. 217—218° (Found: C, 77·4; H, 4·6; N, 11·6%). 1′ : 2-Dimethylpyrazolo-(5′ : 4′ : 3′-1 : 13 : 9)anthrone was insoluble in aqueous sodium hydroxide, and it was reduced with difficulty with alkaline sodium dithionite. It gave an orange solution in concentrated sulphuric acid. The greenish-yellow solution in pyridine became yellow with a green fluorescence on the addition of methanolic potassium hydroxide.

(f) *Phenylmagnesium bromide.* In a similar experiment 10 g. of 1′-methylpyrazolo-(5′ : 4′ : 3′-1 : 13 : 9)anthrone and the Grignard reagent from magnesium (15 g.), bromobenzene

(70 g.), and ether (400 c.c.) gave 5 g. of material, m. p. 190°, and m. p. 240—244° after recrystallisation from benzene (Found : C, 80·6; H, 4·5; N, 9·2. $C_{21}H_{14}ON_2$ requires C, 81·3; H, 4·5; N, 9·0%). This *1′-methyl-x-phenylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone* gave a deep violet solution in concentrated sulphuric acid. On the addition of water the solution became green. The yellow solution in pyridine changed to dark green on the addition of methanolic potassium hydroxide. In other respects the derivative resembled 1′ : 2-dimethylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone.

(g) *Potassium hydroxide.* 1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (3 g.) was stirred into a melt of potassium hydroxide (30 g.) and potassium acetate (5 g.) at 170°. The temperature was raised to 280—300° for 2 hr., then lowered. The resulting melt was added to water and boiled, and the brown solution was filtered and acidified. The brown precipitate (1·9 g.) was dissolved in sodium carbonate solution (charcoal), recovered by acidification, and extracted with acetone, and the soluble fraction (m. p. 200—204°) was crystallised from chlorobenzene. The pure 3-*o*-carboxyphenyl-1-methylindazole, m. p. 205° (Found : C, 71·1; H, 4·6; N, 11·5. Calc. for $C_{15}H_{12}O_2N_2$: C, 71·4; H, 4·7; N, 11·1%), was identical with the compound having the same m. p. prepared by Bradley and Geddes by the action of potassium hydroxide and manganese dioxide on (I; R = R′ = H). When 0·5 g. was heated with 20 c.c. of concentrated sulphuric acid at 100° for 1 hr. 1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone, m. p. 179—180°, resulted.

The portion of the hydrolysis product which did not dissolve in acetone gave a yellow solution and a blue fluorescence in aqueous potassium hydrogen carbonate. In aqueous potassium hydroxide the fluorescence was green.

(h) *Potassium hydroxide in* tert.*-butyl alcohol.* Potassium hydroxide (2 g.) and 0·5 g. of (I; R = R′ = H) were ground together and then refluxed with 20 c.c. of *tert.*-butyl alcohol. The solution, initially yellow-brown, changed to reddish-brown; after 4 hours' heating it was green. The cooled solution was added to water and aerated, and the yellow-brown precipitate was collected, washed, dried (m. p. 240°), and extracted (Soxhlet) with acetone. 1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone dissolved first, then the extract became pale yellow with a green fluorescence, and evaporation gave di-[1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthron-2-yl], m. p. 356—357° (Found : C, 76·5; H, 4·0; N, 12·3. Calc. for $C_{30}H_{18}O_2N_4$: C, 77·0; H, 3·9; N, 12·0%). This compound did not result when the proportion of potassium hydroxide employed was smaller, or when *tert.*-butanol was replaced by alcohol, ethylene glycol, diethylene glycol, 2-methoxyethanol, or diethylene glycol monoethyl ether. Refluxing 2 g. of (I; R = R′ = H) with 4 g. of sodium in 50 c.c. of methanol for 5 hr. gave only unchanged (I). Similarly, only unchanged reagents were recovered when (I; R = R′ = H) (4·7 g.), potassium hydroxide (2·5 g.), and 2-aminoanthraquinone (4·4 g.) were heated with dimethylaniline (100 c.c.) for 8 hr. at 110—120°, and when (I; R = R′ = H) (4·7 g.), potassium hydroxide (2·5 g.), and 2-aminoanthraquinone (4·4 g.) were heated with dimethylaniline (100 c.c.) for 8 hr. at 110—120°. When (I) (4·7 g.), potassium hydroxide (10 g.), and 2-aminoanthraquinone (4·4 g.) were heated at 160—180°, with the addition of sufficient potassium acetate to keep the melt mobile, unchanged reagents and indanthrone resulted.

Action of Reagents on (II; R = R′ = H).—(a) *Sodamide–morpholine.* Equimolar amounts of sodamide (1·9 g.), (II; R = R′ = H) (11·9 g.), and morpholine (50 c.c.) were refluxed for 7 hr. The dark, tarry product was added to ice, and the brown resinous solid which separated was collected, dried, and extracted with concentrated hydrochloric acid. The bases so separated were chromatographed from benzene on alumina. The least strongly adsorbed fraction contained unchanged (II), m. p. 220—222°. The most strongly adsorbed was orange. On elution it gave 1′-methyl-2-morpholinopyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone, m. p. 274—275°, not depressed by the authentic compound.

The acid-insoluble fraction was extracted with acetone. A soluble fraction consisting of (II; R = R′ = H) was obtained and reddish-brown insoluble material. This was purified by making it into a paste with pyridine, adding 20% sodium hydroxide, heating to 70° and finally adding sodium dithionite. A blue solution resulted. This was filtered, the filtrate was aerated, and the orange-brown precipitate was collected, digested with acetone and then crystallised (m. p. >360°) from a large volume of chlorobenzene (Found : C, 75·9; H, 3·9; N, 12·2. Calc. for $C_{30}H_{18}O_2N_4$: C, 77·0; H, 3·9; N, 12·0%). It was identical in properties with di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl] (IV).

(b) *Sodamide–piperidine.* Experiment (a) was repeated with the substitution of piperidine for morpholine; a similar crude product resulted. The acid-soluble fraction gave a bright bluish-red band and a more mobile dark brown band when it was chromatographed from benzene

on alumina. Elution with acetone afforded a solid, m. p. 110—120°, from the red band, and an orange solid, m. p. 220—224°, from the brown band. The second was not depressed by 1′-methyl-2-piperidinopyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone, m. p. 228°, prepared from piperidine and 2-bromo-1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone.

The acid-insoluble fraction was di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl], m. p. >360° (Found : C, 76·7; H, 4·3; N, 11·9%).

(c) *Sodioaniline.* This reagent, prepared from sodium (10 g.), aniline (500 c.c.), copper bronze (0·1 g.), and nickel oxide (0·1 g.), reacted with (II; R = R′ = H) to give only di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl]. No anilino-derivative of (II) could be found. In the following experiments an attempt was made to estimate the rate of the self-coupling reaction.

1′-Methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (10 g.) was dissolved in aniline (100 c.c.) and at a determined temperature the solution was added to a stirred solution of sodioaniline at the same temperature, prepared as above from sodium (10 g.). After an interval a measured volume was withdrawn, added to 10% hydrochloric acid, and kept for several hours. The resulting suspension was filtered, the solid was washed, then dried, and finally extracted with acetone. The Table shows the results obtained in four experiments.

Temp.	Volume withdrawn (V) (c.c.)	Time (min.)	Wt. of solid in volume (V)	
			Insol. in HCl (g.)	Insol. in HCl and insol. in acetone (g.)
186°	40	2	1·210	0·680
		5	1·520	0·670
		10	2·280	0·730
		15	1·300	0·690
		20	1·190	0·700
145	60	2	0·985	0·770
		6	0·935	0·815
		10	0·906	0·800
		15	1·190	0·830
		20	1·390	0·800
106	40	2	1·170	0·650
		3	1·130	0·560
		8	1·030	0·560
		13	1·210	0·540
		30	1·100	0·550
50	40	2	0·850	0·150
		5	0·915	0·290
		10	1·005	0·400
		15	0·955	0·450
		25	1·105	0·460

(d) *Potassium hydroxide and acetophenone.* Potassium hydroxide (60 g.) and 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (10 g.) were ground together, and dry pyridine (200 c.c.) was added, and finally acetophenone (20 c.c.). The mixture was stirred at 30—40° for 2 days during which the colour changed from yellow-brown, through green, to blue. After addition to alcohol (400 c.c.) the whole was poured on ice, and the resulting solution was boiled for 5 hr. The colour changed to brown; on cooling, a tar separated. This solidified when kept, and was then washed with dilute hydrochloric acid and finally extracted with acetone. The residue (4 g.; m. p. >350°) was di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl] (Found : C, 76·7; H, 4·1; N, 12·3. Calc. for $C_{30}H_{18}O_2N_4$: C, 77·0; H, 3·9; N, 12·0%).

The same product was obtained when acetone or acetonitrile was used instead of acetophenone in the above experiment.

(e) *Methylmagnesium bromide.* 1′-Methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (10 g.) was added in portions to a stirred solution of the Grignard reagent prepared from methyl bromide (50 g.), magnesium (12 g.), and ether (500 c.c.). A green colour developed and this changed to blue when the solution was refluxed for 6 hr. After addition to dilute acetic acid (300 c.c. of 30%) the colour changed to yellow-orange. Steam distillation gave a residual brown tar, and this was collected, dried, and digested with cold benzene. The product (Found : C, 76·5; H, 3·9; N, 12·2%) showed the properties of di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl].

A similar product (1 g.) (Found : N, 12·3%) was obtained when the Grignard reagent used in the above experiment was replaced with one prepared from bromobenzene (70 g.), magnesium (15 g.), and ether (400 c.c.).

(f) *Sodium methoxide.* 1′-Methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (2 g.) was refluxed

for several days with a solution prepared from sodium (3 g.) and methanol (50 c.c.). The colour changed rapidly to reddish orange and after several days to deep brown. The product was di-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl] (Found : N, 12·2%).

The same product resulted when 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (2 g.) was stirred at 230—240° for 2 hr. with potassium hydroxide (10 g.), or when 1′-methylpyrazolo-(3′ : 4′ : 5′-1 : 13 : 9)anthrone (0·5 g.) was refluxed with potassium hydroxide (0·5 g.) in *tert.*-butyl alcohol (20 c.c.) for 1·5 hr. The same result was obtained when the solvent was ethyl alcohol, ethylene glycol, diethylene glycol, 2-methoxyethanol, or diethylene glycol monoethyl ether.

(g) *Other reagents.* There was no evidence of a reaction when 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (II) was treated under the following conditions : (i) Potassium carbazole (3·5 g.) was finely ground with 4 g. of (II) and heated in dimethylaniline (100 c.c.) at 120—130° for 9 hr. (ii) Potassium hydroxide (2·5 g.), 2-aminoanthraquinone (4·4 g.), and 4·7 g. of (II) were heated in dimethylaniline (150 c.c.) at 140—150° for 6 hr. In a somewhat similar experiment potassium hydroxide (10 g.) and potassium acetate (1 g.) were melted together, 2-aminoanthraquinone (4·4 g.) and (II) were added, and the whole was stirred for 3 hr. at 200° : the only product isolated was indanthrone.

Action of Potassium Hydroxide and Manganese Dioxide on 1′-Methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone. Formation of a Hydroxy-derivative of 3-o-Carboxyphenyl-2-methylindazole.—An intimate mixture of manganese dioxide (10 g.) and 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)-anthrone (10 g.) was stirred at 240—250° for 2·5 hr. with potassium hydroxide (50 g.) and potassium acetate (5 g.). The product was cooled, boiled with water (1 l.), and filtered, and the residue was further extracted with dilute potassium hydroxide. The combined filtrates were acidified and the brown precipitate was collected, dried (m. p. 235—240°), and extracted with acetone. The solution afforded a solid. This was purified by dissolution in aqueous sodium carbonate (charcoal), re-precipitation (3 g.; m. p. 240°), and crystallisation from acetone (m. p. 190—198°) (Found : C, 67·5; H, 4·7; N, 10·5. $C_{15}H_{12}O_3N_2$ requires C, 67·1; H, 4·4; N, 10·4%). This *monohydroxy*-derivative of 3-*o*-carboxyphenyl-2-methylindazole dissolved in potassium hydrogen carbonate solution with a yellow colour and a green fluorescence; in potassium hydroxide the fluorescence was blue.

Replacement of Halogens in Derivatives of (I) *and* (II). *Reactions of 2-Bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone.*—(a) *Morpholine.* On being refluxed with morpholine (25 c.c.) for 3 hr. 2-bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (0·5 g.) afforded a reddish-orange solution which changed to brown. Addition to water gave a product which was then chromatographed from benzene on alumina. Three bands were formed. The lower yellow band, eluted with acetone, gave *1′-methyl-2-morpholinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)-anthrone*, m. p. 218° (Found : C, 71·1; H, 5·8; N, 13·1. $C_{19}H_{17}O_2N_3$ requires C, 71·4; H, 5·3; N, 13·1%).

(b) *Piperidine.* In a similar experiment in which piperidine (25 c.c.) was used for 7 hr. the product was chromatographed from chlorobenzene on alumina. Two bands formed. The lower, dark red band eluted with acetone gave *1′-methyl-2-piperidinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone*, m. p. 240° (Found : N, 13·3. $C_{20}H_{19}ON_3$ requires N, 13·2%). It dissolved in concentrated sulphuric acid with an orange colour. The reddish-orange solution in pyridine was unaffected by the addition of methanolic potassium hydroxide.

3-Bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone.—Prepared from 1 : 3-dibromoanthraquinone and methylhydrazine and crystallised from chlorobenzene this compound had m. p. 248—249° (Found : C, 58·4; H, 3·1; N, 9·0; Br, 25·7. Calc. for $C_{15}H_9ON_2Br$: C, 57·5; H, 2·8; N, 9·0; Br, 25·5%). Bradley and Geddes (*loc. cit.*) record m. p. 242—244°. It did not react with morpholine at the b. p.

Reactions of 4-Bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone.—This compound, m. p. 249—250° (Found: C, 57·1; H, 2·6; N, 9·1; Br, 25·5. Calc. for $C_{15}H_9ON_2Br$: C, 57·5; H, 2·8; N, 9·0; Br, 25·5%), was prepared by Bradley and Geddes's method (*loc. cit.*). (a) *Morpholine.* After refluxing for 5 hr. a solution of 4-bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)-anthrone (1 g.) in morpholine (50 c.c.), initially orange, became red. Addition to water gave a solid from which after collection, washing, drying (1 g., m. p. 190—200°), and recrystallisation from chlorobenzene, *1′-methyl-4-morpholinopyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone* was obtained as orange needles, m. p. 236° (Found : C, 71·1; H, 5·4; N, 13·1%). It gave a pale yellow solution in both concentrated sulphuric acid and alkaline sodium dithionite. (b) *Piperidine.* In a similar experiment with piperidine (50 c.c.) the yield of crude product was 1 g., and the m. p. was 185—195°. Crystallisation from chlorobenzene afforded *1′-methyl-4-piperidino-*

pyrazolo(5′ : 4′ : 3′-1 : 13 : 9)*anthrone*, m. p. 207—208° (Found : C, 75·9; H, 6·2; N, 12·9%). (c) *Sodioaniline*. 4-Bromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (3 g.) was heated at 60—80° for 4 hr. with a solution of sodioaniline prepared from sodium (1 g.), aniline (30 c.c.), dimethylaniline (30 c.c.), copper bronze (0·1 g.), and nickel oxide (0·1 g.). On addition of the mixture to dilute hydrochloric acid (200 c.c.) the product separated as a dark brown solid (2·8 g.). Extraction with benzene gave a soluble fraction, m. p. 180—200°, and this when chromatographed from benzene on alumina gave two bands. The more strongly adsorbed band was red, and this after elution with acetone gave 4-*anilino*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone*, m. p. 210° (Found : C, 77·1; H, 4·3; N, 13·1%), as an orange brown solid.

4-*Chloro*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone*.—Prepared by a slight modification of Bradley and Geddes's method (*loc. cit.*) 4-chloro-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)-anthrone was obtained as needles, m. p. 268° (Found : N, 10·2; Cl, 13·0. Calc. for $C_{15}H_9ON_2Cl$: N, 10·4; Cl, 13·2%). The same compound (m. p. 264°) was also obtained by methylation of 4-chloro-1 : 9-pyrazoloanthrone (6 g.) with methyl sulphate (17 g.), sodium hydroxide (7 g.), water (70 c.c.), and alcohol (30 c.c.), followed by chromatography (Found : C, 66·7; H, 3·0; N, 10·7; Cl, 13·6. Calc. for $C_{15}H_9ON_2Cl$: C, 67·0; H, 3·3; N, 10·4; Cl, 13·2%). It gave a bright red solution in concentrated sulphuric acid and when heated with morpholine, piperidine, and aniline it gave the same 4-morpholino-, 4-piperidino-, and 4-anilino-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone as had been prepared from the 4-bromo-compound.

5-*Chloro*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone*.—Prepared by refluxing 1 : 5-dichloroanthraquinone (30 g.), methylhydrazine sulphate (20 g.), anhydrous potassium carbonate (30 g.), and pyridine (200 c.c.) for 12 hr. The solution, deep red initially, changed to yellowish-orange, and when it was cooled a solid separated (20 g.). This could not be obtained in a homogeneous form by crystallisation or chromatography. It was therefore heated for 12 hr. in pyridine (100 c.c.) with methylhydrazine sulphate (3 g.) and anhydrous potassium carbonate (5 g.). A solid, m. p. 320—330°, crystallised on cooling, and when the mother-liquor was added to water 5-*chloro*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone* separated. Crystallisation from chlorobenzene gave the pure derivative, m. p. 254° (Found : C, 66·4; H, 3·6; N, 10·5; Cl, 13·7. $C_{15}H_9ON_2Cl$ requires C, 67·0; H, 3·3; N, 10·4; Cl, 13·2%). It dissolved in concentrated sulphuric acid with a deep red colour.

Recrystallisation of the material, m. p. 320—330°, from chlorobenzene, gave *dimethyldi-pyrazoloanthracene* as fine needles, m. p. 340—344° (Found : C, 73·4; H, 4·5; N, 21·2. $C_{16}H_{12}N_4$ requires C, 73·8; H, 4·6; N, 21·4%).

Reactions. (*a*) Morpholine. When refluxed with morpholine (25 c.c.) for 3·5 hr. 5-chloro-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (1 g.) gave a product which was purified by chromatography from chlorobenzene on alumina. The resulting 1′-*methyl*-5-*morpholino-pyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone* formed orange crystals, m. p. 198—199° (Found : C, 71·2; H, 5·3; N, 13·2%). It dissolved in pyridine with a deep orange colour, but in concentrated sulphuric acid the solution was yellow. (*b*) Piperidine. In a similar experiment in which piperidine (25 c.c.) was used, the resulting orange needles of 1′-*methyl*-5-*piperidinopyrazolo*-(5′ : 4′ : 3′-1 : 13 : 9)*anthrone* had m. p. 210° (Found : C, 75·3; H, 5·9; N, 13·0%). This gave a deep red solution in pyridine and a yellow solution in concentrated sulphuric acid. (*c*) Aniline. When 5-chloro-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (1 g.) was refluxed with aniline (50 c.c.) for 20 hr. a reddish-brown solid separated on cooling, and chromatography from benzene on alumina gave 5-*anilino*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone* as red crystals, m. p. 174—176° (Found : C, 77·2; H, 4·8; N, 12·8%). The 5-anilino-derivative dissolved in pyridine with a red colour, but in concentrated sulphuric acid it formed a yellow solution. An additional amount of less pure material was obtained by addition of original mother-liquor to dilute hydrochloric acid.

8-*Chloro*-1′-*methylpyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone*.—1 : 8-Dichloroanthraquinone (50 g.), methylhydrazine sulphate (30 g.), and dry potassium carbonate (45 g.) were refluxed for 12 hr. in pyridine (300 c.c.). The initial colour was deep reddish-orange but this became yellower at the end of the reaction and a solid (50 g.) separated on cooling. Recrystallisation of this *product* from chlorobenzene afforded yellow needles, m. p. 232—233° (Found : C, 66·8; H, 3·3; N, 10·0; Cl, 13·3%). It dissolved in pyridine with a golden-yellow colour and in concentrated sulphuric acid it formed an orange-red solution.

Reactions. There was no evidence of reaction when 8-chloro-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (1 g.) was refluxed for 7 hr. with morpholine (50 c.c.), for 20 hr. with aniline (50 c.c.), or for 6 hr. with a solution prepared from sodium (2·5 g.) and dry methanol (25 c.c.).

Dibromo-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)*anthrone.*—1′-Methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (5 g.) was refluxed in glacial acetic acid (50 c.c.) while a solution of bromine (30 g.) in the same solvent (20 c.c.) was added gradually. Hydrogen bromide was liberated. On being cooled the solution afforded a bright yellow solid, and this was collected, washed, dried (3 g., m. p. 190—200°), and recrystallised several times from glacial acetic acid. The resulting *dibromo*-derivative, m. p. 289° (Found: C, 45·7; H, 1·9; N, 7·1; Br, 39·6. $C_{15}H_8ON_2Br_2$ requires C, 45·9; H, 2·0; N, 7·1; Br, 40·8%), dissolved in concentrated sulphuric acid with a deep red colour, and in pyridine to form a greenish-yellow solution which changed to orange on the addition of a drop of methanolic potassium hydroxide.

Reactions. (*a*) Morpholine. The dibromo-derivative (1 g.) was refluxed for 4·5 hr. with morpholine (50 c.c.). The solution, initially yellowish-orange, became deep reddish-orange, and on being cooled a solid separated. Crystallisation from chlorobenzene gave orange needles, m. p. 282—283° (Found: C, 57·3; H, 4·1; N, 10·4; Br, 19·9. $C_{19}H_{16}O_2N_3Br$ requires C, 57·2; H, 4·0; N, 10·5; Br, 20·1%). This *bromo-morpholino*-derivative formed a yellowish-orange solution in pyridine and a deep reddish-orange solution in concentrated sulphuric acid. (*b*) Piperidine. In a similar experiment with piperidine (50 c.c.), the product (1 g.) crystallised from chlorobenzene as orange needles, m. p. 228° (Found: C, 60·8; H, 4·8; N, 10·8; Br, 21·0. $C_{20}H_{18}ON_3Br$ requires C, 60·9; H, 4·5; N, 10·6; Br, 20·2%). This *bromo-piperidino*-derivative gave an orange solution in pyridine and a pale yellow solution in concentrated sulphuric acid. (*c*) Aniline. The dibromo-derivative (1 g.) was refluxed for 6 hr. with aniline (75 c.c.). After several days the solution afforded a deep red solid. This was collected, washed with hydrochloric acid, then water, and finally dried (m. p. 223—227°), and chromatographed from benzene on alumina. A single red zone was formed. Elution with acetone gave an *anilino-bromo*-derivative, m. p. 226° (Found: C, 61·9; H, 3·1; N, 10·3; Br, 20·5. $C_{21}H_{14}ON_3Br$ requires C, 62·3; H, 3·4; N, 10·3; Br, 19·8%). It dissolved in concentrated sulphuric acid with a deep red colour. It gave a pale orange solution in pyridine, changed to deep red (violet fluorescence) on the addition of methanolic potassium hydroxide.

2-Bromo-1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)*anthrone.*—This compound was prepared by methylating 2-bromo-1 : 9-pyrazoloanthrone, and by brominating 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone; it had m. p. 234° (Bradley and Geddes, *loc. cit.*, state m. p. 232—234°) (Found: C, 57·4; 57·6; H, 2·8, 3·2; N, 8·9, 8·7; Br, 25·5, 25·5. Calc. for $C_{15}H_9ON_2Br$: C, 57·5; H, 2·8; N, 9·0; Br, 25·5%).

Reactions. (*a*) Morpholine. On being refluxed for 5 hr. with morpholine (50 c.c.), 2-bromo-1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (1 g.) afforded a yellow solid, m. p. 270—275°, raised to 279° (Found: C, 70·8; H, 5·3; N, 13·3. $C_{19}H_{17}O_2N_3$ requires C, 71·4; H, 5·3; N, 13·1%) on recrystallisation from benzene. *1′-Methyl-2-morpholinopyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)*anthrone* affords an orange solution in concentrated sulphuric acid and a bright yellow solution with a green fluorescence in benzene or pyridine. (*b*) Piperidine. In a similar experiment with piperidine (50 c.c.) the crude product, m. p. 180—190°, was brownish-orange. It crystallised from chlorobenzene (green fluorescence) in glistening needles of *1′-methy-2-piperidinolpyrazolo*-(3′ : 4′ : 5′-1 : 13 . 9)*anthrone*, m. p. 228° (Found: N, 13·3. $C_{20}H_{19}ON_3$ requires N, 13·2%). Its solutions in pyridine and concentrated sulphuric acid resembled those of the 2-morpholino-analogue.

5-Chloro-1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)*anthrone.*—5-Chloro-1 : 9-pyrazoloanthrone was prepared by Bradley and Geddes's method (*loc. cit.*). The m. p. of the product after recrystallisation from chlorobenzene was 304° (Found: C, 65·9; H, 2·8; N, 11·1; Cl, 13·6. Calc. for $C_{14}H_7ON_2Cl$: C, 66·0; H, 2·7; N, 11·0; Cl, 13·9%). Methyl alcohol (120 c.c.) was added during 1·5 hr. to concentrated sulphuric acid (200 c.c.) which was cooled in ice-water and stirred. 5-Chloro-1 : 9-pyrazoloanthrone (60 g.) was added, and the temperature was raised to 180° and kept thereat for 4 hr. After being kept 12 hr. the solution was added to water and the greenish-brown precipitate was collected, washed with dilute alcoholic sodium hydroxide, and dried (55 g.). Recrystallisation from chlorobenzene gave material, m. p. 170—180°, and this was chromatographed from benzene on alumina. Two main bands resulted: (*a*) the yellow band on elution with acetone gave 5-chloro-1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone, m. p. 254° (Found: N, 10·3; Cl, 13·4%), not depressed by the authentic derivative prepared from 1 : 5-dichloroanthraquinone and methylhydrazine; (*b*) the orange band on elution with acetone gave 5-chloro-1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone, m. p. 234° (Found: C, 66·7; H, 3·4; N, 10·2; Cl, 13·1%). It dissolved in pyridine with a greenish-yellow colour which was unaffected by the addition of methanolic potassium hydroxide.

Reaction with morpholine. On being refluxed with morpholine (50 c.c.) for 4 hr. 5-chloro-1′-

methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (1 g.) afforded a dark solution from which a deep red solid was precipitated on addition to water. Recrystallisation from chlorobenzene (m. p. 214—216°) followed by chromatography from benzene on alumina gave two bands. The lower, pale orange band was washed through the column and the remaining reddish-orange band was eluted with acetone. The extract gave *1′-methyl-5-morpholinopyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)-*anthrone*, m. p. 217—218° (Found: C, 71·2; H, 5·3; N, 12·9%). It dissolved in pyridine with a reddish-orange colour; in concentrated sulphuric acid it formed a pale yellow slution.

8-*Chloro*-1′-*methylpyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)*anthrone*.—Prepared by the action of hydrazine on 1 : 8-dichloroanthraquinone, 8-chloro-1 : 9-pyrazoloanthrone had m. p. 345° after crystallisation from chlorobenzene and sublimation (Found: C, 66·4; H, 2·8; N, 10·8; Cl, 13·4%). Mohlau (*Ber.*, 1912, **45**, 2244) records m. p. >360°. Bradley and Geddes (*loc. cit.*) give m. p. 246—247°. Methyl alcohol (180 c.c.) was added below 40° and with stirring to concentrated sulphuric acid (200 c.c.), and was followed by 8-chloro-1 : 9-pyrazoloanthrone (80 g.). The temperature was raised to 180° and kept thereat for 4 hr. The cooled solution was added to water and the greenish precipitate was collected, washed, and dried (72 g.). Extraction with benzene gave a soluble portion, m. p. 207—214°, and this was further purified by chromatography from benzene on alumina. The main band was orange; elution with alcohol gave 8-*chloro*-1′-*methylpyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)*anthrone* as a yellow solid, m. p. 225° (Found: C, 67·1; H, 3·1; N, 10·3; Cl, 13·5%). The colour in concentrated sulphuric acid was reddish-orange. It dissolved in pyridine with a yellow colour unchanged on the addition of methanolic potassium hydroxide. The 8-chloro-derivative was recovered unchanged after 8 hours' refluxing with morpholine. Similar negative results were obtained when the reagent was piperidine, aniline, or methanolic sodium methoxide.

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The Chemistry of the Triterpenes and Related Compounds. Part XXII. The Conversion of Lupeol into ψ-Taraxasterol (Heterolupeol).*

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ψ-Taraxasterol (heterolupeol) and δ-amyrenol have been obtained from the product of the action of boiling formic acid on lupeol.

IN continuation of the study of the acidic isomerisation of lupeol and its derivatives, the effect of boiling formic acid has been investigated, following earlier studies by Nojd *Arch. Pharm.*, 1927, **265**, 381) and by Biedebach (*ibid.*, 1943, **281**, 49). Nojd isolated two formates which were hydrolysed to alcohols termed α-*allo*lupeol and β-*allo*lupeol. Biedebach reported the isolation of α-*allo*lupeol and also of a new alcohol, γ-*allo*lupeol, but he could not obtain β-*allo*lupeol, which he suggested was impure α-*allo*lupeol. The constants of γ-*allo*lupeol (m. p. 176—177°; $[\alpha]_D$ +9·8°) and of its acetate (m. p. 268—269°; $[\alpha]_D$ +19·4°) and benzoate (m. p. 269—271°; $[\alpha]_D$ +39·5°) are almost identical with those of germanicol (m. p. 176—177°; $[\alpha]_D$ +6°) and its acetate (m. p. 274°; $[\alpha]_D$ +18°) and benzoate (m. p. 269—270°; $[\alpha]_D$ +39°) (Simpson, *J.*, 1944, 283). In the light of the now known structures of lupeol and germanicol and their inter-relationship (Halsall, Jones, and Meakins, *J.*, 1952, 2682) it may be concluded that γ-*allo*lupeol is germanicol.

In our studies on the isomerisation, lupeol was heated under reflux with formic acid (98—100%) for 2 hours. These conditions are similar to those employed by Biedebach (*loc. cit.*), but, whereas Biedebach apparently obtained a homogeneous mixture, the system remained heterogeneous in the present work; a possible factor affecting the solubility may be the presence of small amounts of water in the formic acid.

The crude formate obtained from the isomerisation was hydrolysed to a mixture of at least two alcohols which could not be separated by chromatography on alumina, and which

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formed mixed crystals of constant melting point. Its constants were not comparable with those of any of the *allo*lupeols isolated by Biedebach or by Nojd. By acetylation of the mixed alcohols and careful chromatography it was possible to obtain two acetates (both $C_{32}H_{52}O$), differing greatly in rotation ($[\alpha]_D$ −24·6° and +52°). The lævorotatory acetate absorbed strongly in the low-wave-length ultra-violet region, indicating the presence of a tetrasubstituted double bond, exocyclic to two rings. This evidence, together with the negative rotation, indicated that the acetate was δ-amyrenyl acetate. On admixture with an authentic sample no depression of melting point occurred.

The other acetate was identified as ψ-taraxasteryl acetate. Its melting point was not depressed on admixture with, and its infra-red spectrum was identical with that of, an authentic sample. The melting point of the acetate from the isomerisation product was a little lower than that recorded in the literature for ψ-taraxasteryl acetate, which was found difficult to reproduce, however, even with authentic samples.

The δ-amyrenol and ψ-taraxasteryl acetates were hydrolysed to their respective alcohols. The melting points of these alcohols were not depressed on admixture with authentic samples, and their infra-red spectra were respectively identical with those of δ-amyrenol and ψ-taraxasterol.

The alcohol mixture obtained by hydrolysis of the initial isomerisation product was oxidised under mild conditions. Separation of the resulting ketones on alumina was very difficult, but two isomeric ketones with widely divergent rotations were isolated, and their constants compared well with those of δ-amyrenone and ψ-taraxastenone. Their identities were proved by mixed melting-point determinations and by infra-red examination.

A comparison of the melting points and rotations of the derivatives of the alcohols derived from lupeol with those of the corresponding derivatives of authentic δ-amyrenol and ψ-taraxasterol is given in the Table. The difficulty of purifying the derivatives of the alcohols obtained from the isomerisation reaction is reflected in small differences between the constants quoted, particularly in the case of ψ-taraxasterol. The formation of δ-amyrenol under vigorous conditions was not unexpected, but the formation of ψ-taraxasterol was less predictable. As its formation is of considerable relevance to a general discussion of the acidic isomerisation of lupeol (following paper) confirmation of its presence in the isomerisation product seemed desirable.

The mixed acetates were oxidised with osmium tetroxide. The product consisted mainly of unchanged acetate, but a small fraction which was strongly adsorbed on deactivated alumina was isolated. By comparison of its infra-red spectrum with that of an authentic sample, this fraction was shown to be ψ-taraxastanetriol 3-acetate.

	Derivatives from isomerisation reaction			Literature values	
	M. p.	$[\alpha]_D$	Mixed m. p.	M. p.	$[\alpha]_D$
δ-Amyrenol	210—212°	−46·5°	210—213°	212—212·5°	−50·5° [1]
δ-Amyrenyl acetate	206—207	−24·5	209—210	207·5—209	−34 [1]
δ-Amyrenone	198—201	− 3	199—203	199·5—202·5	−12 [1]
ψ-Taraxasterol	202—215	+46	200—213	217—219	+50 [2]
				198—200	+47 [3]
ψ-Taraxasteryl acetate	225—231	+52	226—233	240—241	— [2]
				234—235	+53 [3]
ψ-Taraxastenone	166—168	+81	166·5—171·5	174—175	+81 [4]

[1] Ames, Halsall, and Jones, *J.*, 1951, 450. [2] Lardelli, Krusi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 1159. [3] Burrows and Simpson, *J.*, 1938, 2042. [4] Ames, Beton, Bowers, Halsall, and Jones, following paper.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. The alumina used for chromatography had an activity I—II.

The Action of Boiling Formic Acid on Lupeol.—Lupeol (24 g.) was heated under reflux in formic acid (98—100%; 400 c.c.) for 2 hr. The solution was deep violet in colour, but much undissolved solid was present throughout the reaction. After filtration, the filtrate was diluted with water, and the resulting precipitate combined with the formic acid insoluble material. A portion of the combined precipitates (17·6 g.) was washed with boiling ethanol (800 c.c.) which left an insoluble amorphous material. This sublimed, giving plates, m. p. 220—224°. The

washings yielded needles (m. p. after sublimation, 215—225°) on cooling. These were filtered off and combined with the insoluble material. The mixture was hydrolysed by heating under reflux with 5% ethanolic potassium hydroxide (300 c.c.). Dilution with water and acidification with dilute sulphuric yielded a solid which was crystallised from ethanol giving needles, m. p. 182—183·5°, $[\alpha]_D$ +3° (*c*, 1·0) (Found: C, 84·5; H, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). Light absorption: $\varepsilon_{2100\ A}$ = 5900, $\varepsilon_{2150\ A}$ = 3500, $\varepsilon_{2200\ A}$ = 1960, and $\varepsilon_{2230\ A}$ = 1430.

A portion (0·65 g.) was chromatographed on alumina (100 g.). All the fractions obtained melted at temperatures between 180° and 190°.

Acetylation of the Mixed Alcohols and Separation of the Mixed Acetates.—The mixed alcohols (1·0 g.) were dissolved in pyridine (25 c.c.), acetic anhydride (25 c.c.) was added, and the mixture was kept at 20° for 16 hr. The solution was evaporated to dryness with methanol, and then the solid was taken up in methanol and the evaporation repeated. After several repetitions of the process the solid finally obtained (1·09 g.) was adsorbed from light petroleum on alumina (100 g.) and eluted as follows [each fraction was eluted with 250 c.c. of solvent; with fractions 1—9 this was light petroleum; fractions 10 and 11 were eluted with light petroleum–benzene (9 : 1)].

Fraction	Wt., mg.	M. p.	Form	Fraction	Wt., mg.	M. p.	Form
1 + 1*a*	17	187—196°	Rods	7	50	212·5—223°	Needles
2	220	202—205·5	,,	8	44	215—226·5	,,
3	184	205·5—208·5	,,	9	77	218—230	,,
4	146	198—204	Needles	10	67	218—231	,,
5	112	202—213	,,	11	25	200—216	,,
6	90	210—221	,,				

Fractions 2 and 3 were combined and crystallised from ethanol, giving δ-amyrenyl acetate as platelets, m. p. 206—207°, $[\alpha]_D$ −24·5° (*c*, 0·6) (Found: C, 82·35; H, 11·15. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Light absorption: $\varepsilon_{2100\ A}$ = 9500, $\varepsilon_{2150\ A}$ = 6000, $\varepsilon_{2200\ A}$ = 3550, and $\varepsilon_{2230\ A}$ = 2600. The m. p. of a mixture with an authentic sample of δ-amyrenyl acetate (m. p. 208°) was 209—210°.

Hydrolysis of the acetate with an ethereal solution of lithium aluminium hydride yielded δ-amyrenol which crystallised from ethanol as needles, m. p. 210—212° undepressed on admixture with an authentic sample (m. p. 213—214·5°), $[\alpha]_D$ −46·5° (*c*, 0·64).

Fractions 4—8 were combined and crystallised from ethanol, giving the mixed acetates as needles (0·27 g.), m. p. 205—210°, $[\alpha]_D$ +19·8° (*c*, 0·5).

Fraction 9 crystallised from ethanol to give ψ-taraxasteryl acetate as plates, m. p. 225—231° $[\alpha]_D$ +52° (*c*, 0·89) (Found: C, 81·75; H, 11·2. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Light absorption $\varepsilon_{2100\ A}$ = 3000, $\varepsilon_{2150\ A}$ = 1300, $\varepsilon_{2200\ A}$ = 340, and $\varepsilon_{2230\ A}$ = 50. The m. p. of a mixture with an authentic sample of ψ-taraxasteryl acetate (m. p. 238—240°) was 226—233°.

Hydrolysis of the acetate with an ethereal solution of lithium aluminium hydride yielded ψ-taraxasterol, which crystallised from ethanol and nitromethane as needles, m. p. 202—215°, $[\alpha]_D$ +46° (*c*, 0·94). The m. p. of a mixture with an authentic sample (m. p. 206—212°) was 200—213°.

Fraction 10 was crystallised from methanol, yielding plates, m. p. 200—228°, $[\alpha]_D$ +61·5° (*c*, 0·70). The constants indicate that the fraction was mainly ψ-taraxasteryl acetate, with possibly a small amount of lupenyl-I acetate.

Oxidation of the Mixed Alcohols and Separation of the Mixed Ketones.—The mixed alcohols (0·47 g.) were kept at 20° for 2 hr. with Kiliani's reagent (120 c.c.) [chromic acid (1·5 g.), acetic acid (120 c.c.), acetone (225 c.c.), and water (15 c.c.)]. Dilution with water and extraction with ether yielded an oil (0·45 g.) which crystallised from ethanol to give needles (0·42 g.), m. p. 183°. These were adsorbed from light petroleum on alumina (42 g.), and fractions were eluted as follows. (i) With light petroleum (700 c.c.): solid (44 mg.), m. p. 177—195°. (ii) With light petroleum–benzene (19 : 1) (175 c.c.): solid (90 mg.), m. p. 155—190°. (iii) With light petroleum–benzene (19 : 1) (525 c.c.): oil (138 mg.). Fraction (i) was crystallised from ethanol, giving δ-amyrenone as rods, m. p. 198—201° undepressed on admixture with an authentic sample (m. p. 199·5—201·5°), $[\alpha]_D$ −3·2° (*c*, 0·5). Fraction (iii) was crystallised from ethanol, nitromethane, and methanol, giving ψ-taraxastenone as fine needle clusters, m. p. 166—168° undepressed on admixture with an authentic sample (m. p. 170—173°), $[\alpha]_D$ +81° (*c*, 0·2).

The Action of Osmium Tetroxide on the Mixed Acetates.—A solution of osmium tetroxide (303 mg.) in dry ether (15 c.c.) was added to a solution of the mixed acetates (0·79 g.) in dry ether (20 c.c.). After 7 days at 20° the reaction mixture was shaken with a solution of mannitol (14 g.) and potassium hydroxide (1·4 g.) in water (140 c.c.) for 8 hr. From the ethereal phase a solid residue (0·726 g.), m. p. 179—197°, was obtained. It was adsorbed from light petroleum

on deactivated alumina (75 g.). After elution with light petroleum (750 c.c.) of a fraction (0·496 g.) consisting of unchanged mixed acetates, elution with ether (500 c.c.) gave an amorphous residue (60 mg.) which was crystallised from nitromethane, giving *ψ-taraxastanetriol 3-acetate* as needles, m. p. 278° (transition to short needles at 240°), $[\alpha]_D$ +41·5° (Found: C, 76·25; H, 10·95. $C_{32}H_{54}O_4$ requires C, 76·25; H, 10·95%). An authentic sample (m. p. 276°) of ψ-taraxastanetriol 3-acetate was prepared from pure ψ-taraxasteryl acetate in a similar manner, and on admixture of the two samples of triol 3-acetate no depression of melting point was found.

One of the authors (R. E. H. S.) is indebted to the Ministry of Education for a F.E.T.S. grant. Thanks are also due to Mr. E. S. Morton and Mr. H. Swift for the microanalyses.

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The Chemistry of the Triterpenes and Related Compounds. Part XXIII. The Structure of Taraxasterol, ψ-Taraxasterol (Heterolupeol), and Lupenol-I.*

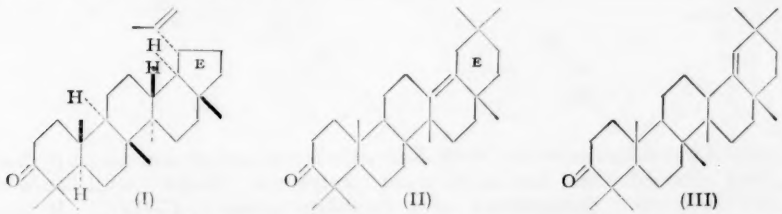
By T. R. AMES, J. L. BETON, A. BOWERS, T. G. HALSALL, and E. R. H. JONES.

[Reprint Order No. 4816.]

The elucidation of the structures of the pentacyclic triterpenes, taraxasterol, ψ-taraxasterol (heterolupeol), and lupenol-I has been completed. Acidic isomerisation of lupeol and its derivatives has given, under various conditions, compounds of the lupenol-I, ψ-taraxasterol, germanicol, and δ-amyrin types. It is now possible to interpret all of these reactions in a rational manner.

Some reactions of lupene-I and the corresponding alcohol and ketone are described.

THE pentacyclic triterpene, lupenone (I), is isomerised by 15% sulphuric acid in acetic acid to δ-amyrenone (II) and by 6% sulphuric acid in the same solvent to lupenone-I. This is also converted into δ-amyrenone under more strongly acidic conditions (Ames, Halsall, and Jones, *J.*, 1951, 450).



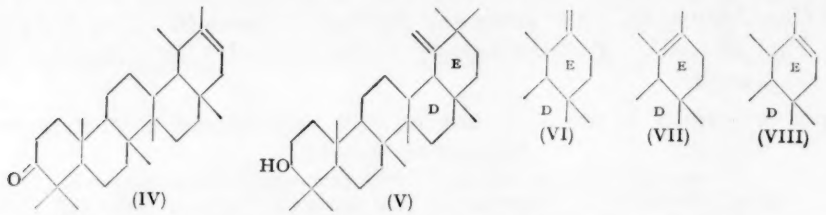
Lupenone-I has a trisubstituted double bond (Ames *et al.*, *loc. cit.*) but the obvious structure which accommodates this fact and the isomerisation to δ-amyrenone is that of germanicone (III) (Barton and Brooks, *J.*, 1951, 257), which is not identical with lupenone-I. It is necessary, however, to consider for lupenone-I a structure with a six-membered ring E since ring enlargement is known to occur even when lupenone is treated with very mild acidic reagents. For example formic acid–benzene at 20° gave 19α-formyloxy-18α-oleanan-3-one (Ames, Davy, Halsall, and Jones, *J.*, 1952, 2868). The most probable structure was (IV) and in the light of the suggested structures for taraxasterol (V or VI) and ψ-taraxasterol (heterolupeol) (VII or VIII) (Dietrich and Jeger, *Helv. Chim. Acta*, 1950, **33**, 711; cf. "Elsevier's Encyclopaedia of Organic Chemistry," Vol. 14 S, pp. 1157 S *et seq.*) it appeared possible directly to correlate lupenone-I and its derivatives with the corresponding compounds of the taraxasterol and ψ-taraxasterol series. This possibility was emphasised when it was found that some ψ-taraxasterol was formed on boiling lupeol in formic acid (Halsall, Jones, and Swayne, preceding paper).

It has been shown that taraxasteryl acetate can be isomerised to lupenyl-I acetate

* Part XXII, preceding paper.

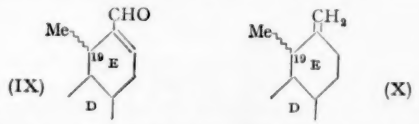
(cf. Barton and Bruun, *J.*, 1952, 1683) by using more vigorous conditions (6% sulphuric acid in acetic acid) than those (10% ethanolic sulphuric acid in benzene) already known to isomerise taraxasteryl acetate to ψ-taraxasteryl acetate (Lardelli, Krüsi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 1815). The latter acetate, as well as the corresponding benzoate and hydrocarbon, have also been converted by *ca.* 6% sulphuric acid in acetic acid into lupenol-I derivatives.

Oxidation of both taraxastene and ψ-taraxastene with selenium dioxide leads to the same αβ-unsaturated aldehyde, heterolupenal (Lardelli *et al.*, *loc. cit.*), which has maximum light absorption in *cyclo*hexane at 2300 Å ($\varepsilon = 13{,}900$) and in ethanol at 2340 Å. Lupene-I underwent a similar oxidation to give a different αβ-unsaturated aldehyde (lupenal-I) with a maximum in *cyclo*hexane at 2285 Å ($\varepsilon = 12{,}300$). These values are in accord with



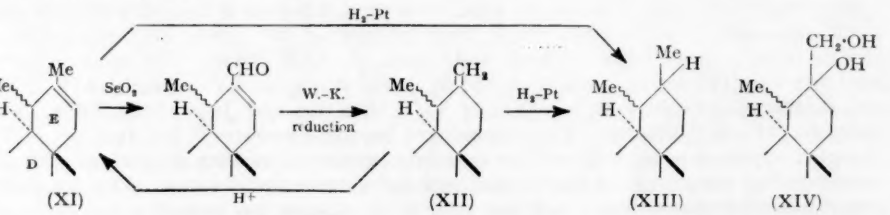
(IV) (V) (VI) (VII) (VIII)

those expected for an αβ-disubstituted αβ-unsaturated aldehyde, but they preclude the possibility of the ethylenic linkage being tetrasubstituted. Thus, *cyclo*hexenealdehyde shows maximum absorption in ethanol at 2290 Å whilst 2-methyl*cyclo*hexenealdehyde and β-*cyclo*citraldehyde absorb at much longer wave-lengths, *viz.*, 2420 and 2490 Å, respectively (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). The structures for heterolupenal and lupenal-I consistent with these results are the two stereoisomers of (IX), differing in the configuration of the $C_{(19)}$-methyl group. If this deduction is correct then taraxastene, obtained from heterolupenal by Wolff–Kishner reduction (Lardelli *et al.*, *loc. cit.*), should be one of the two isomers of structure (X), and its $C_{(19)}$-epimer should be obtainable from lupenal-I by similar reduction.



(IX) (X)

Lupenal-I was subjected to the Wolff–Kishner reaction, and an amorphous hydrocarbon $C_{30}H_{50}$ was obtained which had an infra-red spectrum in "Nujol" with bands at 886, 1647, and 3075 cm.$^{-1}$ characteristic of a vinylidene group (>C=CH$_2$). It appeared, therefore, that this hydrocarbon was indeed the $C_{(19)}$-epimer of taraxastene (*iso*lupene-I). On hydrogenation it gave lupane-I in *good* yield, and it afforded lupene-I on isomerisation with acid. These results are consistent with partial structures (XI), (XII), and (XIII) for lupene-I, *iso*lupene-I, and lupane-I.



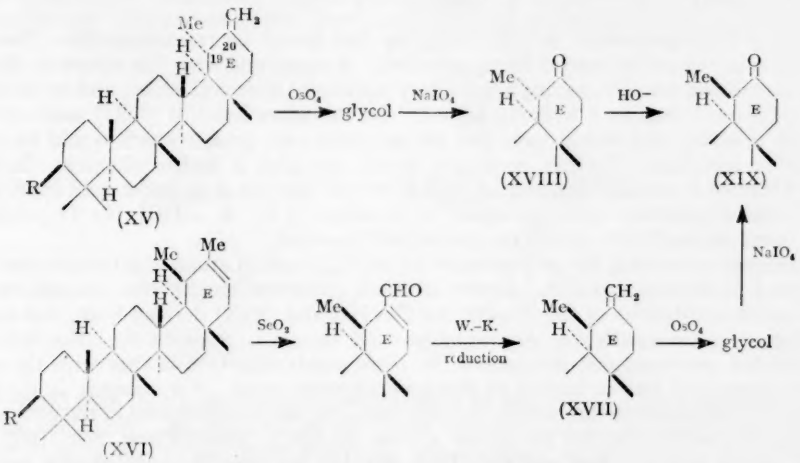
(XI) (XII) (XIII) (XIV)

When, however, the Wolff–Kishner reduction product was treated with osmium tetroxide, some lupane-I was isolated (20% yield), in addition to the expected glycol (XIV), which was obtained in 75% yield. The reduction product is therefore a mixture

of *iso*lupene-I and the corresponding saturated hydrocarbon, lupane-I. Although the reduction was not investigated in great detail it appeared that the amount of lupane-I formed was dependent on the temperature of the reduction. Other examples are known of the complete reduction of an αβ-unsaturated carbonyl system. For instance, cholest-5-en-7-one is reduced to a mixture of cholest-6-ene and cholestane (*ca.* 45%) (Fischer, Lardelli, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 1577).

The glycol (XIV) from *iso*lupene-I was oxidised with sodium periodate and gave a nor-ketone, the infra-red spectrum of which exhibited a band at 1710 cm.$^{-1}$ in both carbon tetrachloride and carbon disulphide, characteristic of a keto-group in a six-membered ring. This proves that the vinylidene group in *iso*lupene-I is also in the same-sized ring, and as *iso*lupene-I gives lupane-I on hydrogenation it follows that the latter and lupene-I both have a six-membered ring E. Treatment of the nor-ketone with methylmagnesium iodide and decomposition of the complex with sulphuric acid gave back lupene-I.

Taraxastene is oxidised by osmium tetroxide to a glycol (Lardelli *et al.*, *loc. cit.*) which is different from that from *iso*lupene-I. Fission of this second glycol with sodium periodate gave a different nor-ketone. Its infra-red spectrum exhibited bands at 1703 and 1706 cm.$^{-1}$ in carbon tetrachloride and carbon disulphide, respectively. When, however, it was adsorbed from benzene on to " neutralised " alumina (of activity I; pH 7—8) it epimerised to the nor-ketone already obtained from *iso*lupene-I. The sequence of reactions leading from taraxastene (XV; R = H) and lupene-I (XVI; R = H) to the

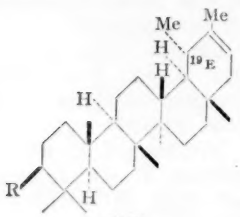


same ketone (XIX; R = H) is summarised in the scheme. It makes it clear that one carbon atom of ring E of the basic ring system must be common to the double bonds of taraxastene and lupene-I and, since the lupene-I double bond is trisubstituted, this common atom is $C_{(20)}$ and not $C_{(19)}$. Further, taraxastene and lupene-I must differ at $C_{(19)}$, having the methyl groups in the epimeric positions. Since the nor-ketone (XVIII) from taraxastene isomerises to that (XIX; R = H) from *iso*lupene-I (XVII), the $C_{(19)}$-methyl group in taraxastene may be regarded as being in the less stable conformation. At first this was assumed to be the axial (polar) conformation (cf. Beton, Bowers, Halsall, and Jones, *Chem. and Ind.*, 1953, 847), but in the light of arguments put forward by Professor D. H. R. Barton and Dr. W. Klyne (cf. *Chem. and Ind.*, 1953, 1386) and discussed later in this paper, we now believe that the weight of evidence and opinion points to the less stable conformation being equatorial, leading to (XV; R = H) for taraxastene and (XVI; R = H) for lupene-I.

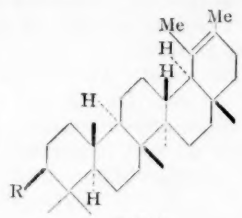
For ψ-taraxasterol the results so far described do not distinguish conclusively between structures (XX; R = OH) and (XXI; R = OH), containing tri- and tetra-substituted double bonds, respectively. However, with heterolupenal established as one of the

stereoisomers of (IX), (XX; R = OH) was strongly favoured for ψ-taraxasterol and final proof was obtained as follows.

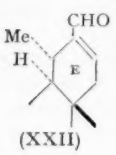
The infra-red spectra of ψ-taraxastene (in "Nujol"), ψ-taraxasterol, ψ-taraxasteryl acetate, and ψ-taraxasteryl formate (all in carbon disulphide) and of heterolupenal (XXII) exhibit bands at 779, 778, 780, 779, and 782 cm.$^{-1}$ respectively, indicative of a trisubstituted double bond. Further the short wave-length ultra-violet spectra of ψ-taraxastene and of lupene-I, which has a trisubstituted double bond, are very similar, both showing a rapid falling off in intensity between 2150 and 2250 Å. This is to be contrasted with the much more gradual intensity decrease for 1 : 2-dimethyl*cyclo*hexene (detailed values are given in the experimental section). Finally ψ-taraxastene was oxidised with osmium tetroxide to a diol (heterolupanediol; Jeger, Krüsi, and Ruzicka, *Helv. Chim. Acta*, 1947,



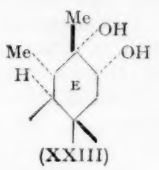
(XX)



(XXI)



(XXII)



(XXIII)

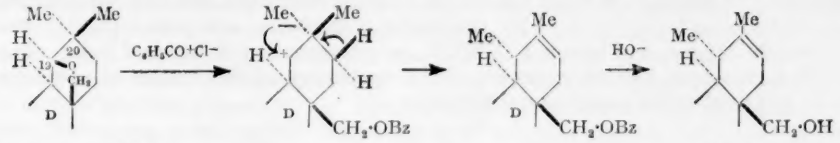
30, 1048). If ψ-taraxasterol is (XX) then the diol would be taraxastane-20α : 21α-diol (XXIII), α-attack of the reagent being assumed. A compound with this structure should form a monoacetate easily, having a secondary equatorial hydroxyl group, and be oxidised under mild conditions to a hydroxy-ketone. On the other hand, if (XXI) were correct then the resulting diol would have two tertiary hydroxyl groups which would be very difficult to acetylate. Further, oxidation would not give a hydroxy-ketone. In fact the diol formed a monoacetate and on oxidation with chromic acid under mild conditions gave a hydroxy-ketone. ψ-Taraxasterol is therefore (XX; R = OH), the $C_{(19)}$-methyl group being assumed to be in the equatorial conformation.

A decision concerning the conformation of the $C_{(19)}$-methyl group in ψ-taraxastene and in lupene-I is not easy to make. Evidence on this point was sought from a consideration of the relative stabilities of the nor-ketones (XVIII) and (XIX) derived from, and corresponding stereochemically to, ψ-taraxastene and lupene-I, respectively. Normally in α-substituted *cyclo*hexanone derivatives the more stable structure is that with the substituent equatorial, but exceptions to this generalisation occur. For instance, in the case of 2-bromo*cyclo*hexanone interaction between the C–Br and C=O dipoles in the equatorial conformation makes this the less stable system (Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301). Again Barton (*Chem. and Ind.*, 1953, 664) has discussed the stability of a number of polyalkylated *cyclo*hexanes and has shown that in certain cases a substituent may be more stable in the axial (polar) than in the equatorial conformation. In the two nor-ketones, whilst the axial (polar) conformation involves a non-bonded interaction between the $C_{(19)}$ and $C_{(17)}$ axial (polar) methyl groups, the equatorial conformation (cf. XVIII) involves *similar* interaction, probably of the same order of magnitude, between the $C_{(19)}$-methyl and the $C_{(12)}$-methylene groups. This suggests that the difference in stability between the two conformations may be small and that any prediction on these grounds concerning the conformation of the more stable isomer is not justified.

More definite evidence is provided by a consideration of the mechanism of formation from *allo*betulin (XXIV) (Davy, Halsall, Jones, and Meakins, *J.*, 1951, 2702) of heterobetulin (Dischendorfer and Grillmayer, *Monatsh.*, 1926, **47**, 419), the 28-hydroxy-derivative of ψ-taraxasterol (Lardelli, Krüsi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 1159). The most plausible mechanism appears to be that indicated, initiated by attack on the ether-oxygen atom by benzoyl chloride ($PhCO^+$ ion). The benzoate is formed by fission of the $C_{(19)}$–O bond and simultaneously a replacement reaction (S_N2) occurs at $C_{(19)}$ with the $C_{(20)}$ axial (α) methyl group becoming attached to $C_{(19)}$ in the *equatorial* conformation.

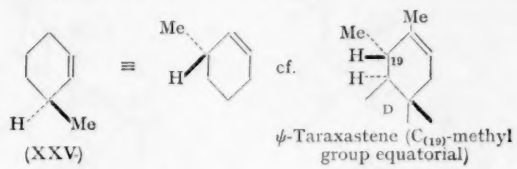
A proton is then expelled from $C_{(21)}$. Now since heterobetulin has been simply converted into ψ-taraxasterol (Lardelli *et al.*, *loc. cit.*) these considerations strongly suggest that the $C_{(19)}$-methyl group in ψ-taraxasterol, and hence in taraxasterol and the nor-ketone from taraxastene, is in the equatorial conformation (cf. XV and XVIII). In turn it follows that the $C_{(19)}$-methyl group in lupene-I, and in the more stable nor-ketone (XIX), is in the axial (polar) conformation.

Evidence in favour of this conclusion has been provided by Dr. W. Klyne from the molecular-rotation differences between ψ-taraxasterol and lupenol-I derivatives. If ψ-taraxastene is (XX; R = H) and lupene-I is (XVI; R = H) with the $C_{(19)}$-methyl group in the axial conformation, then ψ-taraxastene can be regarded as a derivative of

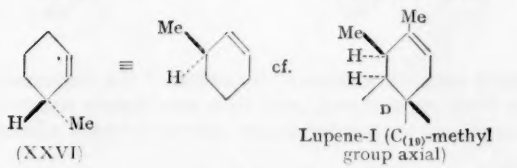


*allo*betulin (XXIV) heterobetulin

lævo-3-methyl*cyclo*hexene (XXV) and lupene-I as a derivative of *dextro*-3-methyl*cyclo*hexene (XXVI). Mills (*J.*, 1952, 4976) has shown that derivatives of type (XXVI) are more dextrorotatory than those of type (XXV) and that the difference ($\Delta[M_D]$ + 200°) is approximately independent of the presence of additional substituents in the *cyclo*hexene



(XXV) ψ-Taraxastene ($C_{(19)}$-methyl group equatorial)



(XXVI) Lupene-I ($C_{(19)}$-methyl group axial)

ring, provided that they have the same configuration in any pair of 3-methyl*cyclo*hexenes which are compared. As indicated in the Table, lupene-I and its derivatives are more dextrorotatory ($\Delta[M_D]$ + *ca.* 200°) than the corresponding ψ-taraxastene derivatives. This is in agreement with lupene-I being of type (XXVI) rather than of type (XXV) and hence with the axial (β) conformation of the $C_{(19)}$-methyl group.

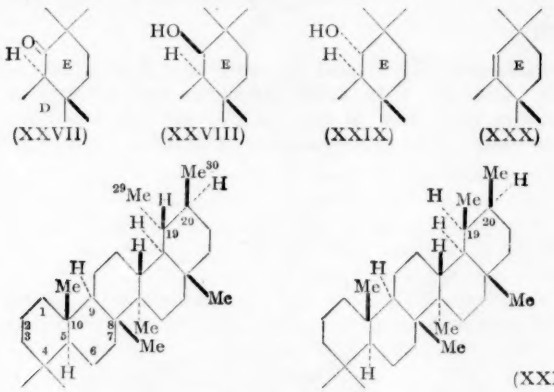
Molecular-rotation differences.

Derivative	$[M]_D$, lupene-I series	$[M_D]$, ψ-taraxastene series	Δ
Hydrocarbon	+418°	+205°	+213°
3β-Hydroxy-	+413	+211	+202
3β-Acetoxy-	+454	+262	+192
3-Oxo-	+534	+344	+190

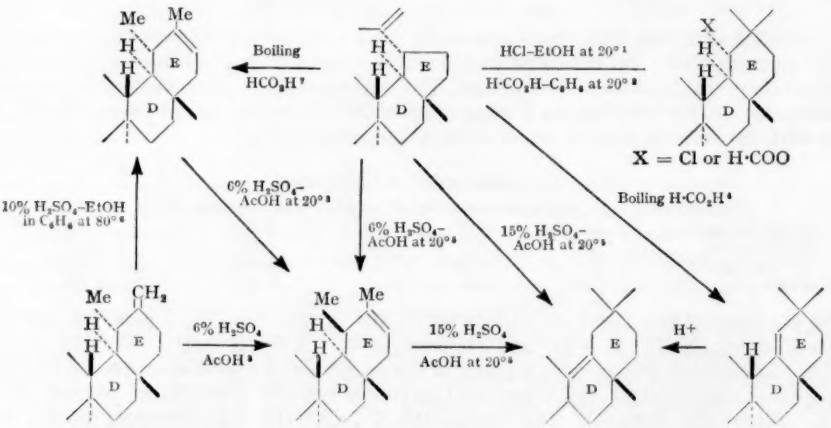
On the basis of the above arguments we incline to the view that lupene-I is correctly represented by (XVI; R = H) and taraxastene by (XV; R = H). Further support for this conclusion is provided by a study of the reduction of 18α-oleanan-19-one (XXVII) with sodium and amyl alcohol when the thermodynamically more stable product should result. From this reduction 18α-oleanan-19β-ol (XXVIII) was obtained in *ca.* 70% yield. It was also formed on reduction of 18α-oleanan-19-one with lithium aluminium hydride. On dehydration with phosphoryl chloride in pyridine it gave germanicene (XXX), elimination occurring between the two *trans* axial groups. In contrast, the isomeric

19α-alcohol (XXIX), prepared by Wolff–Kishner reduction of 19α-hydroxy-18α-oleanan-3-one (Ames, Davy, Halsall, and Jones, *J.*, 1952, 2868), gave α-lupene on similar dehydration. The formation of 18α-oleanan-19β-ol on sodium–alcohol reduction of the keto-compound shows that in *the case of* 18α-*oleanane* a substituent at $C_{(19)}$ is more stable in the *axial* conformation.

With the elucidation of the structures of taraxastene and lupene-I a system of nomenclature for these compounds and their derivatives is proposed based on (XXXI), the structure of taraxastane. This is obtained by hydrogenation of both taraxastene and ψ-taraxastene (see later) and it is reasonable to assume that the hydrogen introduced at $C_{(20)}$ attaches itself to the α-face of the planar molecule, the axial β $C_{(17)}$-methyl group preventing hydrogenation from the β-side. Taraxastene thus becomes taraxast-20(30)-ene, and lupene-I (XVI; R = H) 19α(H)-taraxast-20-ene, *iso*lupene-I (XVII) 19α(H)-taraxast-20(30)-ene, and lupane-I (XXXII), α-hydrogenation of lupene-I being assumed, 19α(H)-taraxastane. Other examples of the application of this system of nomenclature are to be found in the experimental section.

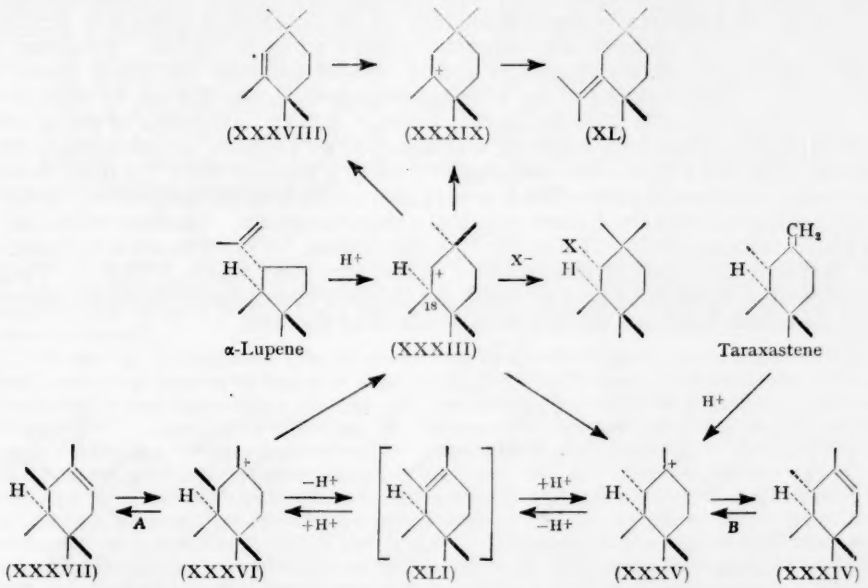


It is now possible to attempt a rational discussion of the isomerisation of lupenol and its derivatives. The products obtained, with their now known structures and the various reaction conditions employed in their formation, are summarised schematically below.


Boiling
HCO₂H [7]
HCl–EtOH at 20° [1]
H·CO₂H–C₆H₆ at 20° [2]
X = Cl or H·COO
10% H₂SO₄–EtOH in C₆H₆ at 80° [6]
6% H₂SO₄–AcOH at 20° [3]
6% H₂SO₄–AcOH at 20° [3]
15% H₂SO₄–AcOH at 20° [5]
Boiling H·CO₂H [4]
6% H₂SO₄ AcOH [5]
15% H₂SO₄ AcOH at 20° [5]
H+

[1] Halsall, Jones, and Meakins, *J.*, 1952, 2862. [2] Ames, Davy, Halsall, and Jones, *ibid.*, p. 2868. [3] This paper. [4] Biedebach, *Arch. Pharm.*, 1943, **281**, 49. [5] Ames, Halsall, and Jones, *J.*, 1951, 450. [6] Lardelli, Krüsi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 1815. [7] Halsall, Jones, and Swayne, preceding paper.

The first stage is ring enlargement to the carbonium ion (XXXIII). In the presence of a large excess of a reactive anion, and under relatively weak acidic conditions, the ring enlargement is accompanied by a concerted stereospecific addition of the anion with the formation of 19α-substituted 18α-oleanane derivatives (cf. Halsall, Jones, and Meakins, *J.*, 1952, 2862; Ames, Davy, Halsall, and Jones, *loc. cit.*). Under more acidic conditions the axial $\alpha C_{(20)}$-methyl group takes the place of the entering anion and participates in a concerted stereospecific rearrangement leading to a 19α-methyl derivative (ψ-taraxastene derivative, XXXIV). This rearrangement involves the formation of the ion (XXXV) and the setting up of the equilibrium *A*. The ψ-taraxastene structure (XXXIV) is thermodynamically less stable than that of lupene-I (XXXVII) to which it isomerises. The isomerisation probably involves (XLI) as a transitory intermediate as indicated. The path proposed involves neither the formation of a secondary carbonium ion nor a carbon–carbon bond fission. Since the lupene-I structure is more stable than that of ψ-taraxastene, lupene-I derivatives will normally be formed, unless the ψ-taraxastene derivative is effectively removed from equilibrium *A*. Two factors may bring this about: insolubility of the ψ-taraxastene compound in the reaction medium and insufficient acid strength to effect proton addition to the double bond of (XXXIV). It is possible that the first factor operates in the formation of ψ-taraxasterol in small yield from lupeol in boiling formic acid and that the second is responsible for the isolation of heterobetulin from *allo*betulin.



The ion (XXXIII), besides undergoing a carbon–carbon rearrangement, can also lose a proton from $C_{(18)}$ to give the germanicol structure (XXXVIII) or rearrange to (XXXIX) which then gives the δ-amyrin skeleton (XL). The formation of δ-amyrin derivatives usually requires strongly acidic conditions (*e.g.*, 15% sulphuric acid in acetic acid). In the case of the conversion of lupene-I derivatives into those of δ-amyrin, the vigorous conditions may be necessary to convert the tertiary ion (XXXVI) into the secondary ion (XXXIII). In this conversion the methyl group which moves is again in the axial conformation.

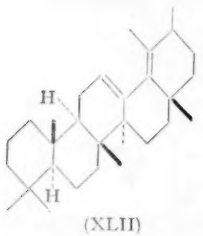
The absence of appreciable amounts of germanicol derivatives in most isomerisations may be due either to the rapid conversion of (XXXVIII) into (XXXIX) or to the direct formation of (XXXIX) from (XXXIII), (XXXVIII) being by-passed. In this connection

it may be of significance that the $C_{(18)}$-hydrogen atom is in the (α)-configuration and so can become attached to $C_{(19)}$ in the α (equatorial) position. This is analogous to the formation of 19α-chloro-18α-oleanan-3β-ol from lupeol.

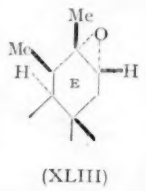
It is of interest that the ion (XXXIII) is postulated by Ruzicka, Eschenmoser, and Heusser as a key intermediate in their scheme for the biogenesis of pentacyclic triterpenes (*Experientia*, 1953, **9**, 357).

So far compounds with the tetrasubstituted double bond structure (XLI) have not been isolated from acidic isomerisations. This is probably due to the instability of this system. Inspection of models of structure (XLI) indicates very great interference between the $C_{(19)}$-methyl group and the $C_{(12)}$-methylene group of ring C. Attention may be drawn to the fact that the isomer of lupeol with the three-carbon side-chain present as an *iso*propylidene group is unknown, and to the lack of reactivity of the keto-group in trisnorlupanone (Davy, Jones, and Halsall, *Rec. Trav. chim.*, 1950, **69**, 368). Both the *iso*propylidene group of the isomer and the keto-group of trisnorlupanone interfere with the $C_{(12)}$-methylene group. Similar interference would be expected between the $C_{(19)}$-methyl and the $C_{(12)}$-methylene group in derivatives of α-amyra-12 : 18-diene (ursa-12 : 18-diene) (XLII?), and it is probably this factor which has prevented the formation so far of such a diene system in the α-amyrin series, although the corresponding system in the β-amyrin series is well known.

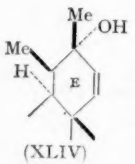
It is now appropriate to describe a number of reactions of lupene-I and its derivatives. Both lupenyl-I acetate and lupenone-I form epoxides when treated with perbenzoic acid. In view of the hindrance to β-attack afforded by the $C_{(17)}$-methyl group it is probable that the oxidation products are α-epoxides (partial structure XLIII). Reduction of each epoxide with lithium aluminium hydride yielded the same diol which formed a monoacetate. Axial opening of the epoxide being assumed, the diol can be formulated as 19α(H)-taraxastane-3β : 20α-diol (partial structure XLIV). Treatment of the epoxide from lupenyl-I acetate with sulphuric acid afforded two products, a monohydroxy conjugated diene and a triol, which was characterised as a monoacetate. The diene showed maximum absorption at 2300—2360 Å (ε = 13,400) and its infra-red spectrum in " Nujol " exhibited a band at 884 cm.$^{-1}$, characteristic of a vinylidene group. The diene is formulated as 19α(H)-taraxasta-20(30) : 21-dien-3β-ol (partial structure XLV). The calculated position of maximum absorption of this structure in the ultra-violet region is 2320 Å. Partial hydrogenation of the diene gave lupenol-I and complete hydrogenation lupanol-I, showing that the carbon skeleton is unchanged on formation of the diene.



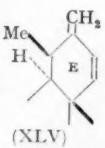
(XLII)



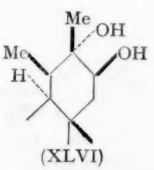
(XLIII)



(XLIV)



(XLV)



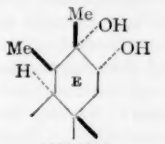
(XLVI)

Acidic fission of an epoxide of a cyclic compound gives a diaxial diol (Barton, *J.*, 1953, 1033). The triol described above is therefore 19α(H)-taraxastane-3β : 20α : 21β-triol (partial structure XLVI). Only the 3β(equatorial)-hydroxyl group should acetylate readily. The formation of a monoacetate is in agreement with this conclusion. The triol is different from that prepared by the action of osmium tetroxide on lupenol-I. This should be the 3β : 20α : 21α-triol and should have two equatorial hydroxyl groups which can be readily acetylated. On acetylation a diacetate was in fact obtained.

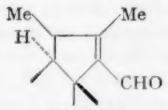
The α-glycol grouping introduced when osmium tetroxide reacts with lupene-I to give a diol (Ames, Halsall, and Jones, *loc. cit.*) should be *cis* (cf. XLVII), and should have one axial and one equatorial hydroxyl group. α-Attack of the reagent again being assumed, the diol should be 19α(H)-taraxastane-20α : 21α-diol (partial structure XLVII). The

21α-hydroxyl group, being secondary and equatorial, should acetylate readily; on acetylation of the diol a monoacetate is formed. Oxidation of the diol with lead tetra-acetate gave a product, $C_{30}H_{48}O$, which formed a 2 : 4-dinitrophenylhydrazone. The formula corresponds to the fission of the glycol to a dicarbonyl derivative followed by cyclisation with elimination of one molecule of water. The most likely cyclisation would appear to lead to (XLVIII).

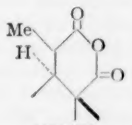
The ultra-violet spectrum of the lead tetra-acetate product shows maximum absorption at 2560—2580 Å and 3200—3400 Å (ε = 13,100 and 150, respectively). The position of maximum absorption is at a somewhat longer wave-length than that calculated by adding, to allow for an additional β-methyl substituent, an increment of 120 Å to the value 2360—2380 Å, which is the wave-length at which *cyclo*pent-1-enealdehyde ($\varepsilon_{max.}$ = 13,500) shows maximum absorption (Brown, Henbest, and Jones, *J.*, 1950, 3624). The *cyclo*pentene



(XLVII)



(XLVIII)



(XLIX)

ring, however, in the lead tetra-acetate fission product is very much more heavily substituted than that of *cyclo*pent-1-enealdehyde. Proof of the presence of an aldehyde group was obtained by further oxidation of the lead tetra-acetate product with chromic acid. A neutral and an acidic fraction were obtained. The latter was methylated with diazomethane to a methyl ester, $C_{31}H_{50}O_2$, with an ultra-violet spectrum characteristic of an αβ-unsaturated ester ($\lambda_{max.}$ 2270—2290 Å, ε = 8800). The neutral fraction did not absorb in the ultra-violet above 2150 Å and gave an analysis in agreement with $C_{28}H_{41}O_3$. One possible structure is the anhydride (XLIX). The investigation of the nature of this compound was not pursued further.

Experimental

Rotations were determined in chloroform at room temperature unless otherwise stated. M. p.s were determined on a Kofler block and are corrected. The alumina used for chromatography had an activity I—II. Light petroleum refers to the fraction with b. p. 60—80° unless otherwise stated.

Isolation of Taraxasterol [*Taraxast-20(30)-en-3β-ol*].—Extraction of chamomile flowers (Belgium first picking) (2·25 kg.) with ether (12 l.) at 20° for 3 days afforded a green oil (75 g.) which was heated under reflux for 4 hr. with potassium hydroxide (60 g.), ethanol (400 c.c.), benzene (200 c.c.), and water (100 c.c.). Extraction of the reaction mixture with ether yielded a yellow solid (20 g.) which was adsorbed from benzene on alumina (activity II; 600 g.). Elution with benzene gave a pale yellow wax (4·12 g.), m. p. 30—40°. Further elution with ether–methanol (4 : 1) yielded a pale yellow amorphous solid (16·1 g.), acetylation of which afforded taraxasteryl acetate [taraxast-20(30)-en-3β-yl acetate] (3·7 g.) as plates (from chloroform–methanol), m. p. 246—248°, $[\alpha]_D$ +100° (*c*, 0·97). Hydrolysis of the acetate with methanolic potassium hydroxide gave taraxasterol as needles (from chloroform–methanol), m. p. 217—220°, $[\alpha]_D$ +92·5° (*c*, 1·4). Benzoylation of taraxasterol with benzoyl chloride and pyridine at 100° gave taraxasteryl benzoate [taraxast-20(30)-en-3β-yl benzoate] as plates (from ethyl acetate–ethanol), m. p. 241—243°, $[\alpha]_D$ +106° (*c*, 0·35).

Isomerisation of Taraxasteryl Acetate to Lupenyl-I Acetate [*19α(H)-Taraxast-20-en-3β-yl Acetate*].—Taraxasteryl acetate (500 mg.) was dissolved in benzene (5 c.c.) and acetic acid (20 c.c.), and sulphuric acid (1·25 c.c.; *d* 1·84) in acetic acid (5 c.c.) was added. The solution became brown and developed a green fluorescence. After 3 days at 18° a white solid (310 mg.) had crystallised and was filtered off. Several crystallisations from chloroform–methanol afforded lupenyl-I acetate as plates, $[\alpha]_D$ +97° (*c*, 0·64), m. p. 241·5—243° undepressed on admixture with an authentic sample (Found: C, 82·1; H, 11·3. Calc. for $C_{32}H_{52}O_2$: C, 82·0, H, 11·2%). The infra-red spectra, determined in "Nujol" suspension, of the crystals and of lupenyl-I acetate were identical. The acetate was further identified by hydrolysis to lupenol-I [19α(H)-taraxast-20-en-3β-ol], $[\alpha]_D$ +96·5° (*c*, 0·54), m. p. 252—253° undepressed on admixture

with an authentic sample. Benzoylation gave lupenyl-I benzoate [19α(H)-taraxast-20-en-3β-yl benzoate], $[\alpha]_D$ +108° (*c*, 0·082), m. p. 273—275° undepressed on admixture with an authentic sample.

Preparation of ψ-Taraxasterol (*Heterolupeol*) (*Taraxast-20-en-3β-ol*).—Taraxasteryl acetate (1·9 g.), benzene (100 c.c.), and ethanol (200 c.c.) were heated under reflux for 5 hr. with concentrated sulphuric acid (20 c.c.). After dilution with water, ethereal extraction yielded a product which was purified by chromatography on alumina and then crystallised from chloroform–methanol, giving ψ-taraxasterol as needles, m. p. 214—216° raised by sublimation to 219—221°, $[\alpha]_D$ +45° (*c*, 1·22) (Found: C 84·55; H 11·8. Calc. for $C_{30}H_{50}O$: C 84·45; H 11·8%). Acetylation of the ψ-taraxasterol in the usual manner afforded ψ-taraxasteryl acetate (taraxast-20-en-3β-yl acetate) as plates m. p. 238—240° (from chloroform–methanol), $[\alpha]_D$ +56° (*c*, 1·24). Benzoylation gave ψ-taraxasteryl benzoate (taraxast-20-en-3β-yl benzoate) as needles, m. p. 273—275° (from ethyl acetate–ethanol), $[\alpha]_D$ +75° (*c*, 1·2).

Preparation of ψ-Taraxastenone (*Taraxast-20-en-3-one*).—ψ-Taraxasterol (1·0 g.) was dissolved in dioxan (50 c.c.) and acetone (100 c.c.) and an 8N-solution of chromic acid in sulphuric acid (3·4 c.c.; 2 mol.) was added. After dilution with water, ethereal extraction yielded a product which was purified by chromatography on alumina and then crystallised from chloroform–methanol, giving *ψ-taraxastenone* (*taraxast-20-en-3-one*) as needles, m. p. 174—175°, $[\alpha]_D$ +81·5° (*c*, 4·4) (Found: C, 85·0; H, 11·4. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%).

Wolff–Kishner Reduction of ψ-Taraxastenone.—ψ-Taraxastenone (7·5 g.), hydrazine hydrate (100 c.c.; 60%), ethanol (400 c.c.), and sodium (20 g.) were heated in an autoclave at 200—240° for 5 hr. under 100 atm. pressure. After dilution with water, ethereal extraction yielded a product which was purified by chromatography on alumina and then crystallised from chloroform–methanol, giving ψ-taraxastene (heterolupene) (taraxast-20-ene) as needles (5 g.), m. p. 182—184°, $[\alpha]_D$ +50° (*c*, 1·37).

Isomerisation of ψ-Taraxasteryl Acetate to Lupenyl-I Acetate.—ψ-Taraxasteryl acetate (1 g.) was dissolved in benzene (10 c.c.) and acetic acid (40 c.c.), and sulphuric acid (3 c.c.; *d* 1·84) in acetic acid (5 c.c.) was added. The mixture was kept at 20° for 60 hr. The crystalline material which had separated was filtered off, washed several times with ethanol, and dried (weight, 680 mg.; m. p. 230—240°). Crystallisation of this product from chloroform–methanol afforded lupenyl-I acetate as plates, m. p. 244—246° undepressed on admixture with an authentic sample, $[\alpha]_D$ +99° (*c*, 1·34). The acetate was further identified by hydrolysis to lupenol-I, m. p. 251—252° undepressed on admixture with an authentic sample, $[\alpha]_D$ +93·5° (*c*, 1·36). Benzoylation of the lupenol-I gave lupenyl-I benzoate, m. p. 273—275° undepressed on admixture with an authentic sample, $[\alpha]_D$ +114° (*c*, 0·58).

Isomerisation of ψ-Taraxasteryl Benzoate to Lupenyl-I Benzoate.—ψ-Taraxasteryl benzoate (120 mg.) was dissolved in benzene (3 c.c.) and acetic acid (5 c.c.), and sulphuric acid (0·25 c.c.; *d* 1·84) in acetic acid (5 c.c.) was added. The mixture was heated to 110°, allowed to cool, and kept at 15° for 45 hr. The white crystalline solid (80 mg.) which separated was filtered off and crystallised from chloroform–methanol, giving lupenyl-I benzoate as plates, m. p. 265—271° undepressed on admixture with an authentic sample, $[\alpha]_D$ +110° (*c*, 1·2).

Isomerisation of ψ-Taraxastene (*Taraxast-20-ene*) *to Lupene-I* [*19α(H)-Taraxast-20-ene*].—ψ-Taraxastene (1·2 g.) was dissolved in benzene (60 c.c.) and acetic acid (120 c.c.), and sulphuric acid (16 c.c.; *d* 1·84) in acetic acid (20 c.c.) was added. After 50 hr. at 20° the crystalline material (660 mg.) which had separated was filtered off, washed with ethanol, and crystallised from ethyl acetate, giving lupene-I as plates, m. p. 223—225° undepressed on admixture with an authentic sample, $[\alpha]_D$ +102° (*c*, 1·39).

Preparation of Taraxast-20(30)-ene.—Taraxast-20(30)-en-3β-one (1·32 g.) [m. p. 182—183·5°, $[\alpha]_D$ +127° (*c*, 0·59)], prepared by oxidising taraxasterol in benzene with a solution of potassium dichromate in dilute sulphuric acid, was heated in an autoclave at 200—240° for 6 hr. with hydrazine hydrate (25 c.c.; 60%) and sodium ethoxide [from sodium (5·4 g.)] in ethanol (100 c.c.). Extraction with benzene yielded a product which was adsorbed from light petroleum on alumina (50 g.; activity II). Elution with light petroleum (750 c.c.) afforded taraxast-20(30)-ene (935 mg.) as needles (several recrystallisations from ethyl acetate), m. p. 209—211°, $[\alpha]_D$ +99° (*c*, 0·3) (Found: C, 87·5; H, 12·4. Calc. for $C_{30}H_{50}$: C, 87·75; H, 12·25%).

Oxidation of 19α(H)-Taraxast-20-ene (*Lupene-I*) *with Selenium Dioxide.*—Lupene-I (560 mg.) in acetic acid–dioxan (1 : 1; 120 c.c.) was heated under reflux with selenium dioxide (600 mg.) for 1 hr. After dilution with water, extraction with benzene afforded a solid (500 mg.) which was adsorbed from light petroleum on alumina (100 g.). Elution with benzene yielded a fraction (220 mg.) which was crystallised from chloroform–methanol giving *30-oxo-19α(H)-taraxast-*

20-*ene* (lupenal-I) as plates, m. p. 277—278°, $[\alpha]_D$ +90° (*c*, 0·51) (Found: C, 84·75; H, 11·7. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%). Light absorption in *cyclo*hexane: Max. 2285 and 3175—3250 Å; ε = 12,300 and 38. In another preparation 30-oxo-19α(H)-taraxast-20-ene was obtained as plates (from ethyl acetate), m. p. 279—281°, $[\alpha]_D$ +95° (*c*, 1·09).

Wolff–Kishner Reduction of 30-*Oxo*-19α(H)-*taraxast*-20-*ene*.—30-Oxo-19α(H)-taraxast-20-ene (1 g.) in diethylene glycol (200 c.c.) was heated under reflux for 1 hr. with hydrazine hydrate (60%; 5 c.c.). Potassium hydroxide (0·8 g.) was added to the cooled mixture, and heating was then continued for a further 6 hr. After dilution with water, extraction with benzene yielded a solid which was adsorbed from light petroleum (200 c.c.) on alumina (50 g.). Elution with light petroleum gave a non-crystalline solid (730 mg.), m. p. 196—206° (from ethyl acetate) raised by many crystallisations from ethyl acetate, chloroform–methanol, and chloroform–acetone to 208—210°, $[\alpha]_D$ −12° (*c*, 1·04). The final product was a mixture of 19α(H)-taraxast-20(30)-ene (*iso*lupene-I) and 19α(H)-taraxastane (lupane-I). The melting point fluctuated slightly on repeated crystallisation (Found, in a typical sample: C, 87·55; H, 12·3. Calc. for $C_{30}H_{50}$: C, 87·75; H, 12·25%. Calc. for $C_{30}H_{52}$: C, 87·3; H, 12·7%). The infra-red spectrum in "Nujol" suspension had bands at 886, 1647, and 3075 cm.$^{-1}$.

Hydrogenation of the Wolff–Kishner Reduction Product from 30-*Oxo*-19α(*H*)-*taraxast*-20-*ene*.—The product (100 mg.) in ethyl acetate (50 c.c.) was shaken with hydrogen for 48 hr. in the presence of Adams platinum catalyst. The resulting product was crystallised from ethyl acetate, giving 19α(H)-taraxastane as plates (70 mg.), m. p. 231—233° undepressed on admixture with an authentic sample, $[\alpha]_D$ +22° (*c*, 0·35).

Isomerisation of the Wolff–Kishner Reduction Product from 30-*Oxo*-19α(H)-*taraxast*-20-*ene*.—The product (103 mg.) in benzene (20 c.c.) was heated under reflux for 5 hr. with ethanolic sulphuric acid (10%; 45 c.c.). After dilution with water, extraction with benzene afforded a crystalline solid which was adsorbed from light petroleum on alumina (25 g.). Elution with light petroleum yielded a fraction (90 mg.) which was crystallised several times from ethyl acetate giving lupene-I, m. p. 223—225° undepressed on admixture with an authentic sample, $[\alpha]_D$ +104° (*c*, 0·75).

Hydroxylation of the Wolff–Kishner Reduction Product from 30-*Oxo*-19α(*H*)-*taraxast*-20-*ene*.—The hydrocarbon mixture (617 mg.) in pyridine–chloroform (1 : 1; 40 c.c.) was treated with osmium tetroxide (400 mg.) and the solution kept at 20° for 7 days. Evaporation of the solvent under reduced pressure gave a dark residue which was heated under reflux for 3 hr. with benzene (13 c.c.), methanol (13 c.c.), and a mixture of potassium hydroxide (3 g.) and mannitol (3 g.) in ethanol (13 c.c.) and water (8 c.c.). After dilution with water, extraction with ether gave a product which was adsorbed from benzene on alumina (50 g.) deactivated by shaking a suspension in benzene with water (5 c.c.). Elution with benzene gave 19α(H)-taraxastane as plates (125 mg.) (from ethyl acetate), m. p. 220—224°, raised by several crystallisations from ethyl acetate to 229—230° undepressed on admixture with an authentic specimen; $[\alpha]_D$ +21°. Elution with benzene–ether (3 : 1; 600 c.c.) gave 19α(*H*)-*taraxastane*-20α : 30-*diol* as plates (500 mg.) (from ethyl acetate), m. p. 257—262° raised by several crystallisations from ethyl acetate to 261—264°, $[\alpha]_D$ +16° (*c*, 1·01) (Found: C, 80·8; H, 11·9. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Oxidative Fission of 19α(*H*)-*Taraxastane*-20α : 30-*diol*.—19α(H)-Taraxastane-20α : 30-diol (319 mg.) in ethanol (100 c.c.) was treated with sodium metaperiodate (300 mg.) in water (5 c.c.) and the solution was kept at 20° for 48 hr. After dilution with water, extraction with ether gave 30-*nor*-19α(H)-*taraxastan*-20-*one* * as needles (250 mg.) (from ethyl acetate), m. p. 225—245° raised by several crystallisations from ethyl acetate to 251—253°, $[\alpha]_D$ +14° (*c*, 1·09) (Found: C, 84·4; H, 11·5. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%). The infra-red spectra in carbon disulphide and carbon tetrachloride both exhibited a strong band at 1710 cm.$^{-1}$. 30-*Nor*-19α(H)-*taraxastan*-20-*one oxime* crystallised as flat needles (from ethyl acetate), m. p. 250—252° (Found: N, 3·15. $C_{29}H_{49}ON$ requires N, 3·3%).

Action of Methylmagnesium Iodide on 30-*Nor*-19α(*H*)-*taraxastan*-20-*one*.—30-Nor-19α(H)-taraxastan-20-one (35 mg.) in ether (50 c.c.) was heated under reflux with excess of methylmagnesium iodide for 30 min. and then kept at 20° for 16 hr. Dilute sulphuric acid was then added (2N; 50 c.c.), and the product was extracted with ether and adsorbed from light petroleum (10 c.c.) on alumina (3 g.). Elution with light petroleum gave 19α(H)-taraxast-20-ene (34 mg.) as plates (from ethyl acetate), m. p. 217—221° raised by several crystallisations from ethyl acetate to 221—223° and then undepressed on admixture with an authentic sample, $[\alpha]_D$ +107° (*c*, 0·95).

* The number prefixing "nor" is that of the carbon atom removed.

Taraxastane-20α : 30-*diol*.—Taraxast-20(30)-ene (2·2 g.) in pyridine–chloroform (1 : 1; 100 c.c.) was treated with osmium tetroxide (1·3 g.), and the solution kept at 20° for 7 days. Evaporation of the solvent under reduced pressure gave a dark residue which was heated under reflux for 3 hr. with benzene (45 c.c.), methanol (45 c.c.), and a mixture of potassium hydroxide (10·5 g.) and mannitol (10·5 g.) in ethanol (45 c.c.) and water (28 c.c.). After dilution with water, extraction with ether yielded a product which was adsorbed from benzene (150 c.c.) on alumina (40 g.). Elution with benzene (500 c.c.) gave taraxast-20(30)-ene (650 mg.). Elution with ether yielded a fraction which was crystallised from ethyl acetate, giving taraxastane-20α : 30-diol as needles (900 mg.), m. p. 233—236° raised by several crystallisations from ethyl acetate to 235—237°, $[\alpha]_D$ +13° (*c*, 0·89). Lardelli *et al.* (*Helv. Chim. Acta*, 1948, **31**, 1815) give m. p. 236—238°, $[\alpha]_D$ +10·5°.

Oxidative Fission of Taraxastane-20α : 30-*diol*.—The diol (360 mg.) in ethanol (175 c.c.) was treated with a solution of sodium metaperiodate (280 mg.) in water (2·5 c.c.), and the solution was kept at 20° for 16 hr. After dilution with water, extraction with ether gave 30-*nortaraxastan*-20-*one* as needles (290 mg.) (from ethyl acetate), m. p. 195—211° raised by several crystallisations from ethyl acetate to 210—213°, $[\alpha]_D$ +65° (*c*, 1·27) (Found: C, 84·3; H, 11·65. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%). The infra-red spectrum in carbon tetrachloride exhibited a strong band at 1703 cm.$^{-1}$, and in carbon disulphide at 1706 cm.$^{-1}$. 30-*Nortaraxastan*-20-*one oxime* crystallised as fine needles, m. p. 217—219°, from ethyl acetate (Found: N, 3·5. $C_{29}H_{49}ON$ requires N, 3·3%).

Epimerisation of 30-*Nortaraxastan*-20-*one to* 30-*Nor*-19α(H)-*taraxastan*-20-*one*.—30-Nortaraxastan-20-one (400 mg.) in benzene (50 c.c.) was adsorbed on alumina (30 g.; activity I; pH 7·5—8·0). Elution with benzene–ether (120 : 1; 700 c.c.) gave a fraction (390 mg.) which was crystallised several times from ethyl acetate, giving 30-nor-19α(H)-taraxastan-20-one as needles, m. p. 252—254° undepressed on admixture with an authentic sample; $[\alpha]_D$ +15° (*c*, 1·19). The infra-red spectrum in carbon disulphide was identical with that of an authentic specimen.

Oxidation of Taraxast-20-*ene* (ψ-*Taraxastene*) *with Selenium Dioxide*.—Taraxast-20-ene (750 mg.) in acetic acid–dioxan (1 : 1; 150 c.c.) was heated under reflux for 2 hr. with a solution of selenium dioxide (750 mg.) in water (5 c.c.) and acetic acid (20 c.c.). After dilution with water, extraction with ether afforded a solid (750 mg.) which was adsorbed from light petroleum on alumina (40 g.; deactivated by addition of 4 c.c. of 10% aqueous acetic acid). Elution with light petroleum yielded a fraction which was crystallised from chloroform–methanol, giving 30-oxotaraxast-20-ene (heterolupenal) as plates (535 mg.), m. p. 226—228°, $[\alpha]_D$ +89° (*c*, 6·88) (Found: C, 84·7; H, 11·45. Calc. for $C_{30}H_{48}O$: C, 84·85; H, 11·4%). Light absorption in *cyclo*hexane: Max. 2300 and 3200—3250 Å; ε = 13,900 and 63·5. Light absorption in ethanol: Max. 2340 Å; ε = 12,500.

Acetylation of Taraxastane-20α : 21α-*diol* (*Heterolupanediol*).—The diol (150 mg.) (m. p. 254—258°; $[\alpha]_D$ +30°), prepared according to Jeger, Krüsi, and Ruzicka's method (*Helv. Chim. Acta*, 1947, **30**, 1048), was dissolved in pyridine (10 c.c.) and heated with acetic anhydride (1 c.c.) at 100° for 2 hr. After dilution with water, extraction with ether yielded a product which was adsorbed from benzene (10 c.c.) on alumina (10 g.). Elution with benzene–ether (4 : 1; 300 c.c.) gave a *monoacetate* which crystallised from methanol as needles, m. p. 204—206°, $[\alpha]_D$ +63° (*c*, 0·54) (Found: C, 79·2; H, 11·35. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%). The monoacetate was converted back to the original diol, m. p. 256—258° undepressed on admixture with an authentic sample, $[\alpha]_D$ +30° (*c*, 1·06), by treatment with ethereal lithium aluminium hydride.

Oxidation of Taraxastane-20α : 21α-*diol* (*Heterolupanediol*).—The diol (150 mg.) in acetone (150 c.c.) was treated with 8N-chromic acid according to the method of Bowers *et al.* (*J.*, 1953, 2555). After dilution with water, extraction with ether yielded a product which was adsorbed from benzene (15 c.c.) on alumina (15 g.; pH 7·5). Elution with benzene–ether (9 : 1; 400 c.c.) gave 20α-*hydroxy*-21-*oxotaraxastane* (90 mg.) as plates (from methanol), m. p. 212—220° raised by several recrystallisations from methanol–chloroform to 221—224°, $[\alpha]_D$ +6° (*c*, 0·57) (Found: C, 81·25; H, 11·45. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). The infra-red spectrum in carbon tetrachloride exhibited bands at 1698 and 3510 cm.$^{-1}$.

20α : 21α-*Epoxy*-19α(*H*)-*taraxastan*-3β-*yl Acetate*.—Lupenyl-I acetate (8·0 g.) in chloroform (140 c.c.) was kept at 6° with perbenzoic acid (1·2 mol.) in chloroform (75 c.c.) for 65 hr. The product, isolated in the usual manner, was adsorbed from benzene (60 c.c.) on alumina (400 g.). Elution with light petroleum–benzene (2 : 3; 400 c.c.), benzene (200 c.c. and 1100 c.c.), benzene–ether (1 : 1; 500 c.c.), and ether (400 c.c.) yielded fractions: (i) (40 mg.), (ii) (0·78 g.), (iii) (4·24 g.), (iv) 0·98 g., and (v) 0·39 g. Fractions (i) and (ii) were unchanged lupenyl-I acetate.

Crystallisation of fractions (iii), (iv), and (v) from chloroform–methanol gave 20α : 21α-*epoxy*-19α(*H*)-*taraxastan*-3β-*yl acetate* as thick platelets (4·16 g.), m. p. 279—281°, $[\alpha]_D^{20}$ +57° (*c*, 1·18) (Found : C, 79·1; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

20α : 21α-*Epoxy*-19α(*H*)-*taraxastan*-3-*one*.—Lupenone-I (4·0 g.) was treated with perbenzoic acid as in the preceding experiment. The product was isolated in the usual manner and adsorbed from benzene on alumina (150 g.). Elution with light petroleum–benzene (3 : 7; 800 c.c.) yielded a fraction which crystallised from chloroform–methanol to give 20α : 21α-*epoxy*-19α(*H*)-*taraxastan*-3-*one* as prisms (2·05 g.), m. p. 242—248°, $[\alpha]_D$ +86° (*c*, 2·1) (Found : C, 81·9; H, 10·8. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%).

Reduction of 20α : 21α-*Epoxy*-19α(*H*)-*taraxastane*-3-*one with Lithium Aluminium Hydride*.—20α : 21α-Epoxy-19α(H)-taraxastan-3-one (2·05 g.) in ether (600 c.c.) containing sodium methoxide [from sodium (0·05 g.) in methanol (1 c.c.)] was treated with lithium aluminium hydride (0·5 g.) in ether (100 c.c.). After the mixture had been kept at 20° for 30 min., sulphuric acid (2N; 100 c.c.) was carefully added with cooling. The product was isolated in the usual manner and adsorbed from benzene (60 c.c.) on alumina (120 g.). Elution with benzene–ether (1 : 1; 1120 c.c.) afforded a solid which was crystallised several times from dioxan–methanol, giving 19α(*H*)-*taraxastane*-3β : 20α-*diol* as prisms (960 mg.), m. p. 302·5—304°, $[\alpha]_D$ +49° (*c*, 2·2) (Found : C, 81·35; H, 11·6. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). When this reaction was carried out in the absence of sodium methoxide, chromatographic separation afforded small and variable quantities of a compound which crystallised from chloroform–methanol as felted needles, m. p. 267—268°, $[\alpha]_D$ +20° (*c*, 0·75) (Found : C, 80·1; H, 11·9%).

The diol (1·05 g.) was acetylated in pyridine (20 c.c.) at 90° with acetic anhydride (10 c.c.) for 2 hr. The product after chromatographic purification (900 mg.) gave, on crystallisation from chloroform–methanol, platelets of 20α-*hydroxy*-19α(*H*)-*taraxastan*-3β-*yl acetate*, m. p. 279—280°, $[\alpha]_D$ +55·5° (*c*, 1·37) (Found : C, 78·8; H, 11·2. $C_{32}H_{54}O_3$ requires C, 78·95; H, 11·2%).

Reduction of 20α : 21α-*Epoxy*-19α(*H*)-*taraxastan*-3β-*yl Acetate with Lithium Aluminium Hydride*.—20α : 21α-Epoxy-19α(H)-taraxastan-3β-yl acetate was reduced with lithium aluminium hydride in the absence of sodium methoxide under similar conditions to those used for the reduction of lupenone-I epoxide. The main product was 19α(H)-taraxastan-3β : 20α-diol together with small quantities (*ca.* 5%) of the compound, m. p. 267—268°, described above.

Acidic Fission of 20α : 21α-*Epoxy*-19α(*H*)-*taraxastan*-3β-*yl Acetate*.—The epoxide (5·5 g.) in ethanol (95%; 960 c.c.) was heated under reflux for 24 hr. with sulphuric acid (2N; 103 c.c.). After dilution with water, extraction with chloroform yielded a solid (5·46 g.) which was adsorbed from benzene (50 c.c.) on alumina (500 g.). Two main fractions were eluted with benzene–ether (7 : 3; 2100 c.c.) (2·82 g.) and ether (1600 c.c.) (2·50 g.). The first crystallised from chloroform–methanol to give 19α(*H*)-*taraxasta*-20(30) : 21-*dien*-3β-*ol* (dehydrolupenol-I) as needles, m. p. 246·5—248°, $[\alpha]_D$ +249° (*c*, 1·65) (Found : C, 84·5; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption in *n*-hexane : Max. 2300—2360 Å; ε = 13,400. Acetylation with pyridine–acetic anhydride, in the usual manner, gave the *acetate* which crystallised from chloroform–methanol as platelets, m. p. 247—249°, $[\alpha]_D$ +230° (*c*, 1·42) (Found : C, 82·35; H, 10·75. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). The infra-red spectrum in " Nujol " had a band at 884 cm.$^{-1}$.

The second fraction did not crystallise satisfactorily. Accordingly a portion (817 mg.) in pyridine (8 c.c.) was kept at *ca.* 90° with acetic anhydride (4 c.c.) for 2 hr. Dilution with water and extraction with chloroform yielded a product which was purified by chromatography on alumina and crystallised from chloroform–methanol, giving 20α : 21β-*dihydroxy*-19α(*H*)-*taraxastan*-3β-*yl acetate* as platelets, m. p. 306—306·5°, $[\alpha]_D$ +47° (*c*, 0·95) (Found : C, 76·4; H, 11·0. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85%). The monoacetate did not absorb ultra-violet light above 2150 Å.

Action of Osmium Tetroxide on Lupenol-I.—Lupenol-I (1 g.) in pyridine–chloroform (1 : 1; 50 c.c.) was treated with osmium tetroxide (1 g.), and the solution kept at 20° for 14 days. Evaporation of the solvent under reduced pressure gave a dark residue which was heated under reflux for 3 hr. with benzene (30 c.c.), methanol (30 c.c.), and a mixture of potassium hydroxide (6 g.) and mannitol (6 g.) in ethanol (30 c.c.) and water (15 c.c.). Sodium sulphite (1 g.) was then added and the mixture refluxed for a further hour. After evaporation of the solvents under reduced pressure, extraction with ether yielded a product which was purified by chromatography on alumina to give a white solid (1 g.). This was crystallised from ethyl acetate to give 19α(*H*)-*taraxastane*-3β : 20α : 21α-*triol* as needles, m. p. 280—282°, $[\alpha]_D$ −6° (*c*, 1·0 in C_5H_5N) (Found : C, 78·45; H, 11·35. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%). The triol (130 mg.)

was acetylated in pyridine (5 c.c.) at 20° with acetic anhydride (2 c.c.) for 20 hr. The product crystallised from methanol to give 3β : 21α-*diacetoxy*-20α-*hydroxy*-19α(*H*)-*taraxastane*, m. p. 281—282°, $[\alpha]_D$ +2° (*c*, 0·9) (Found: C, 74·85; H, 10·3. $C_{34}H_{56}O_5$ requires C, 74·95; H, 10·35%).

Hydrogenation of 19α(*H*)-*Taraxastan*-3-*one* (*Lupenone-I*).—Lupenone-I (650 mg.) in acetic acid (120 c.c.) was shaken with Adams catalyst (325 mg.) and hydrogen at 20° for 18 hr. After filtration and evaporation, crystallisation of the residue from chloroform–methanol gave 19α(*H*)-*taraxastan*-3β-*ol* (lupanol-I) as platelets (560 mg.), m. p. 260—260·5°, $[\alpha]_D$ +12° (*c*, 0·92) (Found: C, 82·6; H, 12·4. $C_{30}H_{52}O,\frac{1}{2}CH_3{\cdot}OH$ requires C, 82·4; H, 12·3%).

Acetylation with pyridine–acetic anhydride in the usual manner gave 19α(*H*)-*taraxastan*-3β-*yl acetate* as platelets (from chloroform–methanol), m. p. 252·5—253°, $[\alpha]_D$ +21° (*c*, 1·68) (Found: C, 81·7; H, 11·4. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%). Benzoylation with benzoyl chloride in pyridine at 20° for 24 hr. gave 19α(*H*)-*taraxastan*-3β-*yl benzoate* as platelets (from chloroform–methanol), m. p. 238—240°, $[\alpha]_D$ +41° (*c*, 0·89) (Found: C, 83·3; H, 10·7. $C_{37}H_{56}O_2$ requires C, 83·4; H, 10·6%).

Partial Hydrogenation of 19α(*H*)-*Taraxasta*-20(30) : 21-*dien*-3β-*ol*.—19α(H)-Taraxasta-20(30) : 21-dien-3β-ol (80 mg.) in acetic acid (100 c.c.) was shaken with 5% palladised charcoal (100 mg.) and hydrogen at 20° for 4 hr. After filtration and evaporation, elution of the residue with benzene–ether (2 : 3; 700 c.c.) from alumina (30 g.) yielded a fraction which crystallised from chloroform–methanol, giving 19α(H)-taraxast-20-en-3β-ol (lupenol-I) as platelets (49 mg.), m. p. 252—254° undepressed on admixture with an authentic sample, $[\alpha]_D$ +86° (*c*, 1·02).

Complete Hydrogenation of 19α(*H*)-*Taraxasta*-20(30) : 21-*dien*-3β-*ol*.—19α(H)-Taraxasta-20(30) : 21-dien-3β-ol (150 mg.) in chloroform (10 c.c.) and acetic acid (40 c.c.) was shaken with Adams catalyst (50 mg.) and hydrogen for 18 hr. at 20°. After filtration and evaporation, crystallisation of the residue from chloroform–methanol gave 19α(H)-taraxastan-3β-ol as platelets (126 mg.), m. p. 261·5—262° undepressed on admixture with an authentic sample prepared by hydrogenation of 19α(H)-taraxast-20-en-3β-ol, $[\alpha]_D$ +13° (*c*, 1·79).

Oxidation of 19α(*H*)-*Taraxastane*-20α : 21α-*diol with Lead Tetra-acetate*.—19α(H)-Taraxastane-20α : 21α-diol (1·34 g.) in chloroform (100 c.c.) and acetic acid (300 c.c.) was treated at 20° with a solution of lead tetra-acetate (1·50 g.; 1·2 mol.) in chloroform (20 c.c.) and acetic acid (70 c.c.). The mixture was warmed to 45° and then, after 15 min. at this temperature, was kept at 20° for 14 hr. After dilution with water, extraction with chloroform afforded a resin which was adsorbed from benzene (30 c.c.) on alumina (200 g.). After development of the chromatogram with benzene (500 c.c.), elution with benzene–ether (7 : 3; 800 c.c.) yielded a solid *product* which crystallised from ethyl acetate–methanol as platelets (960 mg.), m. p. 264—298° (decomp. over range), $[\alpha]_D$ +50° (*c*, 1·19) (Found: C, 84·5; H, 11·2. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption in chloroform: Max. 2560—2580 and 3200—3400 Å; ε = 13,100 and 150.

The 2 : 4-*dinitrophenylhydrazone* of the oxidation product crystallised from chloroform–methanol as red needles, m. p. 274·5—278° (decomp.) (Found: N, 9·3. $C_{36}H_{54}O_4N_4$ requires N, 9·3%).

Oxidation of the Product of the Reaction between 19α(*H*)-*Taraxastane*-20α : 21α-*diol and Lead Tetra-acetate*.—The product (300 mg.) in chloroform (30 c.c.) and acetic acid (150 c.c.) was treated with chromic acid (90 mg.) in 95% acetic acid (11 c.c.) and kept at 20° for 15 hr. After destruction of the excess of oxidising agent with methanol, dilution with water and extraction with chloroform gave a gummy solid which was divided into an acidic and a neutral fraction. The neutral fraction (178 mg.) was adsorbed on alumina. Elution with light petroleum (b. p. 40—60°)–benzene (1 : 9; 600 c.c.) gave starting material (89 mg.). Further elution with benzene–ether (1 : 1) (600 c.c.) gave a fraction (84 mg.) which crystallised from chloroform–methanol to give platelets, m. p. 267·5—268°, $[\alpha]_D$ +30° (*c*, 0·49) (Found: C, 78·9; H, 10·4. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%). The platelets in chloroform gave a pale yellow colour with tetranitromethane. Light absorption in ethanol: ε at 2100 Å = 640, ε at 2150 Å = 430, ε at 2200 Å = 325, and ε at 2250 Å = 275.

The acidic fraction (103 mg.) was treated with ethereal diazomethane, and the product was adsorbed on alumina (30 g.). The fraction (80 mg.) eluted with light petroleum (b. p. 40—60°)–benzene (7 : 3; 400 c.c.) was crystallised from chloroform–methanol, giving platelets, m. p. 237·5—238·5° (Found: C, 81·4; H, 11·0. $C_{31}H_{50}O_2$ requires C, 81·85; H, 11·1%). Light absorption in hexane: Max. 2270—2290 Å; ε = 8800.

The 1 : 2-dimethyl*cyclo*hexene had b. p. 136—138°, n_D^{20} 1·4590, and was prepared by Signaigo and Cramer's method (*J. Amer. Chem. Soc.*, 1933, **55**, 3326).

Reduction of 18α-*Oleanan*-19-*one with Sodium in Amyl Alcohol.*—18α-Oleanan-19-one (380 mg.), prepared by the Clemmensen reduction of 18(α)-oleanane-3 : 19-dione (cf. Ames, Davy, Halsall, and Jones, *J.*, 1952, 2872), was heated under reflux with sodium (10 g.) in boiling amyl alcohol (100 c.c.) for 4 hr. After removal of excess of sodium by addition of

Ultra-violet light absorption in cyclo*hexane of taraxast*-20-*ene*, 19α(*H*)-*taraxast*-20-*ene* (*lupene-I*), *and* 1 : 2-*dimethyl*cyclo*hexene*.

	ε values at					
	2050	2100	2150	2200	2230	2250 Å
Taraxast-20-ene	3800	1600	450	70	20	15
19β(H)-Taraxast-20-ene	4700	2600	1030	140	30	20
1 : 2-Dimethyl*cyclo*hexene	4100	2550	1360	750	540	420

methanol and dilution with water, extraction with ether yielded a product which was adsorbed from light petroleum on alumina (50 g.). After elution with light petroleum (300 c.c.), elution with benzene (200 c.c.) afforded a fraction (300 mg.) which was crystallised from chloroform–methanol, giving 18α-*oleanan*-19β-*ol* as prisms (250 mg.), m. p. 236—237°, $[\alpha]_D$ +31° (*c*, 0·46) (Found : C, 84·3; H, 12·25. $C_{30}H_{52}O_2$ requires C, 84·05; H, 12·25%). On further crystallisation of the compound from the same solvent, platelets, m. p. 229—230°, $[\alpha]_D$ +31·5° (*c*, 0·9), were obtained. The m. p. of a mixture of the two forms was 229—230°.

Dehydration of 18α-*Oleanan*-19β-*ol with Phosphoryl Chloride in Pyridine.*—18α-Oleanan-19β-ol (55 mg.) in pyridine (15 c.c.) was heated under reflux with phosphoryl chloride (2·5 c.c.) for 1 hr. After careful addition of water extraction with ether yielded a product (needles; 50 mg.) which was adsorbed from light petroleum on alumina (20 g.). Elution with light petroleum afforded a fraction (40 mg.) which was crystallised from chloroform–methanol, giving olean-18-ene (germanicene) as fine needles, m. p. 174—174·5° undepressed on admixture with an authentic sample of germanicene kindly supplied by Professor D. H. R. Barton.

Reduction of 18α-*Oleanan*-19-*one with Lithium Aluminium Hydride.*—18α-Oleanan-19-one (162 mg.) in dry ether (70 c.c.) was treated with lithium aluminium hydride (100 mg.) at 20° for 2 hr. After careful addition of water, ethereal extraction yielded a product which was crystallised from chloroform–methanol, giving 18α-oleanan-19β-ol as rhombs (120 mg.), m. p. 231—232° undepressed on admixture with the sample prepared by reduction with sodium in amyl alcohol; $[\alpha]_D$ +29·5° (*c*, 1·22).

Preparation of 18α-*Oleanan*-19α-*ol.*—19α-Hydroxy-18α-oleanan-3-one (Ames, Davy, *et al.*, *loc. cit.*) (0·65 g.), hydrazine hydrate (90%; 2·5 c.c.), and a solution of sodium in ethanol (20 c.c.) were heated in an autoclave for 5 hr. After dilution with water, the product was isolated by filtration and adsorbed from benzene on alumina (50 g.). Elution with benzene–ether (1 : 1; 250 c.c.) gave a fraction (505 mg.), m. p. 222·5—223·5°, which was crystallised from ethanol–chloroform, giving 18α-*oleanan*-19α-*ol* as plates, m. p. 223·5—225°, $[\alpha]_D$ −3° (*c*, 1·6) (Found : C, 83·85; H, 12·05. $C_{30}H_{52}O_2$ requires C, 84·05; H, 12·25%).

Dehydration of 18α-*Oleanan*-19α-*ol with Phosphoryl Chloride in Pyridine.*—18α-Oleanan-19α-ol (130 mg.) in pyridine (5 c.c.) was heated under reflux with phosphoryl chloride (0·5 c.c.) for 2 hr. After careful addition of water, extraction with ether yielded a product (110 mg.) which was crystallised from chloroform–methanol giving α-lupene as needles (80 mg.), m. p. 163—165° undepressed on admixture with an authentic sample, $[\alpha]_D$ +29° (*c*, 0·45).

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Properties and Reactions of Free Alkyl Radicals in Solution. Part VII. Reactions with Quinone Imides, Nitric Oxide, and Nitroso-compounds.*

By Bernard A. Gingras and William A. Waters.

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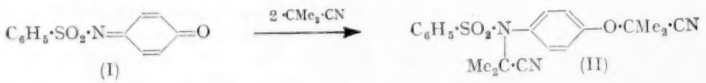
2-Cyano-2-propyl radicals add on to *p*-benzoquinone monobenzenesulphonimide in the same way as they do to quinones (Parts I and V), but corresponding products could not be isolated from acylated quinone di-imides. Nitric oxide and several tertiary nitroso-compounds combine with 2-cyano-2-propyl radicals to form trisubstituted hydroxylamines. On acid hydrolysis these lose one cyanopropyl group with formation of acetone. The aryl-*ON*-di-(2-cyano-2-propyl)hydroxylamines when reduced with zinc dust and acetic anhydride give aryl-*N*-(2-cyano-2-propyl)hydroxylamines, aromatic azo-compounds and arylacetamides, but all in rather poor yield.

2-Cyano-2-propyl radicals do not react with *s*-trinitrobenzene, 2 : 4-dinitrochlorobenzene, or azoxybenzene.

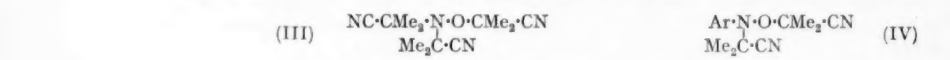
2-Cyano-2-propyl radicals, produced by thermal decomposition of solutions of αα′-azo-*iso*butyronitrile, have been shown to add on to the carbon atoms of easily polymerisable olefins, and to the oxygen atoms of quinones (Part I, *J.*, 1950, 1764; Part V, *J.*, 1952, 4666) but show little or no tendency to add on to isolated C=O groups (Part IV, *J.*, 1952, 3108), to C=N or N=N groups, or to the nitrogen atoms of radicals formed by homolytic halogen abstraction from *N*-halogenoanilides (Part VI, *loc. cit.*).

We have been successful, however, in effecting addition to *p*-benzoquinone monobenzenesulphonimide (I) (Adams and Looker, *J. Amer. Chem. Soc.*, 1951, **73**, 1145) and obtained the expected product (II), which had an infra-red spectrum of requisite character. We failed, however, to demonstrate the occurrence of similar addition to two acylated quinone di-imides, very few of which have sufficient thermal stability to withstand heating to the required temperature.



(I) (II)

Although many aromatic nitro-compounds are effective retarders or inhibitors of vinyl polymerisation, and presumably act by combining somehow with hydrocarbon radicals (Bartlett and Kwart, *ibid.*, 1950, **72**, 1051), we have found that 2-cyano-2-propyl radicals do not react detectably in boiling toluene solution with *s*-trinitrobenzene or 2 : 4-dinitrobenzene, and so must, in this respect, be much less active than triphenylmethyl radicals which at once attack the NO_2 group of nitrobenzene (Hammond and Ravve, *ibid.*, 1951, **73**, 1891). Azoxybenzene also did not react. The N=O bonds of nitro-compounds, however, do not have full double-bond character, and the N⟶O group of azoxybenzene clearly has no unsaturation. The unsaturated N=O group is, however, the characteristically reactive feature of nitroso-compounds, and, as we mentioned in a preliminary note (*Chem.*



(III) (IV)

and Ind., 1953, 615), we have found that 2-cyano-2-propyl radicals react not merely with the odd electron of nitric oxide, but with tertiary nitroso-compounds too, to give the fully substituted hydroxylamines of structures (III) and (IV). Several new compounds of type (IV) are listed in Table 1.

Though it has been known for a long time that nitric oxide reacts with free radicals, Schlenk, Mair, and Bornhardt (*Ber.*, 1911, **44**, 1169) failed to isolate the product formed from triphenylmethyl, which they assumed to be the simple addition compound $Ph_3C·N{:}O$.

* Part VI, *J.*, 1953, 3529.

Weitz, Müller, and Dinges (*Chem. Ber.*, 1952, **85**, 878), however, in a study of the radicals obtained by reducing triphenylmethane dyes, found that the reaction with nitric oxide was much more complex, and succeeded in isolating *NN*-diarylhydroxylamines, $Ar_2N{\cdot}OH$ [Ar = $(Me_2N{\cdot}C_6H_4)_3C$, etc.], in addition to dyes re-formed by the oxidation of the radicals by the nitric oxide.

Hinshelwood and his colleagues (*Proc. Roy. Soc.*, 1937, *A*, **159**, 32) and many later workers have produced kinetic evidence of gas-phase combination of nitric oxide with free methyl and similar radicals but did not establish the initial formation of nitrosomethane. Raley, Rust, and Vaughan (*J. Amer. Chem. Soc.*, 1948, **70**, 88) found that the first stable product of the thermal reaction is formaldoxime, and Coe and Doumani (*ibid.*, p. 1516) succeeded in isolating nitrosomethane and its dimer from the products of vapour-phase photolysis of *tert.*-butyl nitrite at 25°. Chilton and Gowenlock recently (*J.*, 1953, 3232; *Nature*, 1953, **172**, 73) isolated acetoxime and an unidentified nitroso-compound, which they believe to be 2-nitrosopropane, from the gas-phase reaction of nitric oxide with free *iso*propyl radicals, and Haszeldine (*J.*, 1953, 2075) has prepared a series of monomeric nitrosoperfluoroalkanes. None of these workers had envisaged the possibility that nitric oxide itself might combine with more than one free radical.

The assignment of the structure tris-(2-cyano-2-propyl)hydroxylamine (III) to our radical adduct to nitric oxide is in full accord with the infra-red spectrum of our product. On hydrolysis with dilute sulphuric acid it yields acetone, but the *NN*-disubstituted hydroxylamine (V) could not be isolated. Since the same product (III) was also obtained

$$\underset{\text{(III)}}{(NC{\cdot}Me_2)_2N{\cdot}O{\cdot}CMe_2{\cdot}CN} + H_2O \longrightarrow \underset{\text{(V)}}{(NC{\cdot}CMe_2)_2N{\cdot}OH} + HCN + Me_2C{:}O$$

by the action of 2-cyano-2-propyl radicals on nitroso*iso*butyronitrile ($NC{\cdot}CMe_2{\cdot}N{:}O$) (Piloty, *Ber.*, 1898, **31**, 1878), as well as from *N*-nitrosodiphenylamine, which is known to dissociate slowly, $Ph_2N{\cdot}NO \rightleftharpoons Ph_2N{\cdot} + {\cdot}NO$, on heating, there can be little doubt of the disposition of the cyanopropyl groups in our reaction product.

The trisubstituted aromatic hydroxylamines (IV) give one equivalent of acetone on acid hydrolysis, but again the isolation of other pure reaction products was not successful. These hydroxylamines are resistant to reduction by sodium amalgam in aqueous alcohol, sodium dithionite, and hydrogen at up to 5 atm. pressure in the presence of Raney nickel. Reduction with zinc dust in hot acetic acid gave the corresponding unsubstituted *N*-arylacetamide (VIII), which proved that nuclear substitution of the aromatic ring had not occurred. Reduction with zinc dust and acetic anhydride in the presence of sodium acetate gives (VIII) and in most cases also the free secondary hydroxylamine (VI) and the

aromatic azo-compound (VII) though only in small yields. Secondary amines (IX) could not be isolated. The compound (IX; Ar = Ph), however, can be synthesised from aniline, acetone, and cyanide and is easily degraded to acetanilide by treatment with zinc dust and hot acetic acid. The reduction apparently cleaves the C–O rather than the N–O bond.

Few infra-red spectra of hydroxylamine derivatives have hitherto been reported. Table 3 lists the distinctive absorption bands of our products and gives some indication of the covalencies to which they may be due.

Experimental

Reaction between p-*Benzoquinone Monobenzenesulphonimide and* αα′-*Azoisobutyronitrile.*— The sulphonimide (Adams and Looker, *loc. cit.*) (4·94 g., 0·02 mole) and αα′-azo*iso*butyronitrile (3·28 g., 0·02 mole) were dissolved in toluene (50 c.c.) and heated under reflux for 2½ hr. The solvent and tetramethylsuccinonitrile (0·3 g., 11%) were removed by steam-distillation, the

residue was extracted with ether, the extract dried ($MgSO_4$), and the solvent removed. When the residual oil (6·15 g.) was passed through a column of alumina there were obtained *p*-benzenesulphonamidophenol, m. p. 154°, and 4-(2-*cyano*-2-*propoxy*)-N-(2-*cyano*-2-*propyl*)-N-*benzenesulphonanilide* (II) (0·4 g., 6·5%), which crystallized from ether–light petroleum (b. p. 20—40°); m. p. 92—93° (Found: C, 62·9; H, 5·6; N, 10·95; S, 8·3. $C_{20}H_{21}O_3N_3S$ requires C, 62·6; H, 5·4; N, 11·0; S, 8·35%). Its infra-red spectrum showed the typical CN band at 4·48 μ and a band at 12·04 μ, typical of *p*-substituted benzene derivatives, and was generally similar to that of *p*-benzenesulphonamidophenol in the 6·5—9·5 μ region, but had no absorption in the 3 μ region, thus showing absence of OH and NH groups.

No identifiable compounds were obtained from similar reactions with *p*-benzoquinone di-*p*-toluenesulphonimide (Adams and Nagarkatti, *J. Amer. Chem. Soc.*, 1950, **72**, 4601) or *p*-benzoquinone dibenzimide (Adams and Anderson, *ibid.*, p. 5154).

Reaction of Nitric Oxide with 2-Cyano-2-propyl Free Radicals.—A slow stream of nitric oxide, prepared as described by Gatterman ("Laboratory Methods of Organic Chemistry," Macmillan & Co., London, 1938), mixed with dry carbon dioxide, was passed through a gently refluxing solution of αα′-azo*iso*butyronitrile (3·28 g.) in benzene (100 c.c.). At first a deep green colour, indicative of a tertiary nitroso-compound, was formed but this gradually faded. Heating was continued for 2½ hr. to complete the decomposition of the azo-compound and the reaction mixture was then freed from nitric oxide by flushing with a rapid stream of carbon dioxide. The resulting solution was distilled in steam to remove benzene and tetramethylsuccinonitrile, and the residue was extracted with ether, dried ($MgSO_4$), and crystallised from ether–light petroleum (b. p. 20—40°) (yield, 1·54 g., 50%). The *tri*-(2-*cyano*-2-*propyl*)*hydroxylamine* (III) had m. p. 77—78° and was slightly soluble in water (Found: C, 61·4; H, 7·9; N, 23·4. $C_{12}H_{18}ON_4$ requires C, 61·5; H, 7·7; N, 23·9%). It was not affected by warming with dilute aqueous sodium hydroxide, but after refluxing for 8 hr. with 5% sulphuric acid, 50% of the material had decomposed, giving a solution which contained acetone (dinitrophenylhydrazone, m. p. and mixed m. p. 126°) but no products which could be extracted with ether under either acid or alkaline conditions.

*Reaction of Nitroso*iso*butyronitrile with 2-Cyano-2-propyl Radicals.*—A solution of nitroso*iso*butyronitrile (Piloty, *loc. cit.*) (1·95 g.) and αα′-azo*iso*butyronitrile (6·56 g.) in benzene (100 c.c.) was heated under reflux. The blue solution became green after 5 min. and then colourless in 30 min. The heating was continued for 2½ hr. and volatile products were then removed by steam-distillation. The residue (III), after ether extraction and crystallisation, had m. p. and mixed m. p. 78° (yield, 1·1 g., 25%).

TABLE 1. *Tertiary hydroxylamines*, $NC{\cdot}CMe_2{\cdot}NAr{\cdot}O{\cdot}CMe_2{\cdot}CN$.

			Found, %			Required, %		
Ar group	M. p.	Yield, %	C	H	N	C	H	N
C_6H_5	95°	75	69·4	7·0	17·2	69·1	7·0	17·2
o-$Me{\cdot}C_6H_4$	85	70	70·2	7·3	16·3	70·0	7·4	16·3
m-$Me{\cdot}C_6H_4$	74	60	70·2	7·8	16·3	,,	,,	,,
p-$Me{\cdot}C_6H_4$	89	35	70·2	7·7	16·1	,,	,,	,,
o-$Cl{\cdot}C_6H_4$	95	60	60·8	6·0	15·3	60·5	5·8	15·1 *
m-$Cl{\cdot}C_6H_4$	106	47	60·6	5·7	15·0	,,	,,	,, †
p-$Cl{\cdot}C_6H_4$	96	60	60·7	5·7	15·1	,,	,,	,, ‡
s-$Me_3C_6H_3$	122	20	71·8	8·2	14·5	71·6	8·0	14·7

* Found: Cl, 12·8. Required: Cl, 12·8%. † Found: Cl, 12·9%. ‡ Found: Cl, 12·2%.

Reaction between Diphenylnitrosamine and 2-Cyano-2-propyl Radicals.—Diphenylnitrosamine (5·94 g.) and αα′-azo*iso*butyronitrile (9·84 g.) were refluxed in toluene for 2½ hr. After steam-distillation and ether-extraction of the residue there were obtained 3·92 g. (56%) of (III), m. p. and mixed m. p. 78°, together with diphenylamine (m. p. and mixed m.p. 52°). Tetraphenylhydrazine, which yields diphenylnitrogen free radicals when heated, also gives diphenylamine, but no tertiary amine, when heated in solution with αα′-azo*iso*butyronitrile (personal communication from Dr. M. C. Ford).

Reactions of Aromatic Nitroso-compounds with 2-Cyano-2-propyl Radicals.—The nitroso-compounds were prepared by the general method of Lutz and Litton (*J. Org. Chem.*, 1937, **2**, 68). The following preparation is typical. αα′-Azo*iso*butyronitrile (16·4 g., 0·1 mole) and nitrosobenzene (5·35 g., 0·05 mole) were refluxed in toluene (200 c.c.) for 2½ hr. The green colour of the nitroso-compound disappeared in a few minutes and the solution became yellow. After steam-distillation, the residue, which was partly soluble in water, was extracted with ether, dried ($MgSO_4$), and crystallised by addition of light petroleum (b. p. 20—40°).

TABLE 2.

	Secondary hydroxylamines, Ar·N(OH)·CMe_2·CN							Azo-compounds, ArN:NAr	Arylacetamides, Ar·NHAc
		Found, %			Required, %				
Ar group	M. p.	C	H	N	C	H	N	M. p.	M. p.
C_6H_5	77°	68·3	6·8	15·8	68·2	6·8	15·9	66°	114°
o-Me·C_6H_4	66	(identified by its infra-red spectrum showing OH band at 3·07 μ)						55	110
m-Me·C_6H_4 ...	72	69·5	7·5	14·7	69·5	7·4	14·7	55	65
m-Cl·C_6H_4	98	57·8	5·5	13·3	57·0	5·2	13·3 *	99	72
p-Cl·C_6H_4	76	57·2	5·2	13·1	57·0	5·2	13·3 †	188	176

* Found: Cl, 17·1. Required Cl, 16·9%. † Found: Cl, 16·7%.

TABLE 3. *Absorption bands taken from the infra-red spectra of* (III) *and compounds listed in Tables* 1 *and* 2 *in the* 7·5—12 μ *region.*

[All these compounds show bands at 4·5 μ (CN group) and at 7·22 and 7·33 μ (CMe_2 group). The secondary hydroxylamines (VI) also show bands at 3·0—3·1 μ (OH group).] *

Wave-lengths, μ:	7·5—8	8—8·5	8·5—9	9—9·5	9·5—10	10—10·5	10·5—11	11—12
$(CMe_2·CN)_2N·O(CMe_2·CN)$	—	8·24 s	8·60 s	—	9·84 m	10·14 m	10·65 w	11·04 m
		8·42 m	8·77 s	—	—	10·50 s	10·75 s	11·98 s
Tertiary hydroxylamines (IV)								
Ar = Ph	7·80 m	8·19 m	8·59 s	9·30 s	9·78 w	10·00 w	10·65 w	11·15 m
		8·35 s	—	—	9·85 s	10·12 w	10·99 s	11·45 s
						10·41 s	—	11·83 m
Ar = *o*-Me·C_6H_4	7·76 m	8·15 m	8·51 s	9·00 s	9·51 m	10·30 s	10·52 w	11·07 m
		8·24 m	8·60 s	—	9·59 m	—	10·78 w	11·35 s
		8·40 s	—	—	9·83 m	—	—	11·60 w
Ar = *m*-Me·C_6H_4	7·64 w	8·04 m	8·51 s	9·15 m	9·61 w	10·03 w	10·57 m	11·25 s
		8·17 s	8·62 s	—	9·75 m	10·37 s	10·68 m	11·39 m
		8·31 s	—	—	—	—	10·95 s	11·88 s
		8·40 s						
Ar = *p*-Me·C_6H_4	7·82 w	8·15 m	8·60 s	—	9·62 w	10·30 m	10·58 w	11·05 w
		8·26 w	8·98 s	—	9·87 m	10·39 m	10·79 w	11·40 s
		8·35 s	—	—	—	—	—	11·95 m
		8·45 m	—	—	—	—	—	—
Ar = *o*-Cl·C_6H_4	7·94 m	8·20 s	8·64 s	9·48 s	9·65 s	10·35 s	10·76 m	11·08 m
		8·24 m	—	—	9·85 m	10·45 s	—	11·40 s
		8·36 s	—	—	—	—	—	11·60 m
Ar = *m*-Cl·C_6H_4	7·75 w	8·17 w	8·60 s	9·18 m	9·80 m	10·02 m	10·74 s	11·10 w
	7·88 w	8·35 s		9·30 s	—	10·38 s	—	11·35 s
Ar = *p*-Cl·C_6H_4	7·86 m	8·20 w	8·58 s	9·06 m	9·82 w	10·47 s	10·65 w	11·12 s
		8·26 w	8·65 s	9·20 s	9·90 s	—	10·82 w	11·45 s
		8·35 m	—	—	—	—	—	11·95 s
Ar = *s*-$Me_3C_6H_3$	—	8·13 m	8·52 s	—	9·64 m	10·20 s	10·61 w	11·10 m
		8·23 m	8·60 s	—	9·82 m	10·33 m	10·69 w	11·40 s
		8·37 w	—	—	—	10·45 m	10·76 w	11·58 s
Secondary hydroxylamines (VI)								
Ar = Ph	7·65 s	8·04 m	8·55 s	9·25 w	9·72 s	10·31 w	10·62 s	11·18 s
	7·75 w	8·20 s	8·67 w	—	9·82 s	—	—	11·57 s
		8·40 s	—	—	9·97 w	—	—	11·96 w
Ar = *o*-Me·C_6H_4	7·68 s	8·04 s	8·57 s	—	9·56 s	10·15 m	10·56 s	11·25 s
	—	8·19 s	8·97 s	—	9·76 s	—	10·68 w	11·31 w
		8·35 m	—	—	9·90 w	—	10·76 w	11·45 s
		8·43 m	—	—	—	—	—	11·70 w
Ar = *m*-Me·C_6H_4	7·75 s	8·20 s	8·53 s	9·13 m	9·70 s	10·03 w	10·63 s	11·40 s
	7·95 s	8·39 s	—	—	9·97 w	10·50 s	—	11·55 m
Ar = *m*-Cl·C_6H_4	7·68 s	8·03 s	8·57 s	9·15 s	9·74 s	10·06 s	10·59 s	11·45 m
	7·93 s	8·21 s	—	9·35 s	9·97 w	10·10 w	10·80 m	11·65 s
		8·38 s	—	—	—	10·27 w	—	—
Ar = *p*-Cl·C_6H_4	7·68 m	8·06 s	8·51 w	9·17 s	9·67 s	—	10·56 s	11·25 s
	7·77 m	8·18 s	8·55 s	—	9·95 s	—	—	11·44 m
		8·29 s	8·97 m	—	—	—	—	—

* s = Strong absorption; m = moderate absorption; w = weak absorption.

The tertiary hydroxylamines were insoluble in aqueous alkali but dissolved in warm dilute mineral acids. *ON*-Di-(2-cyano-2-propyl)-*N*-phenylhydroxylamine (8 g.) was refluxed for 8 hr. in 10% hydrochloric acid (300 c.c.). The solution had then darkened considerably. From a 10-c.c. sample of the aqueous solution, there was isolated 0·13 g. of acetone 2 : 4-dinitrophenylhydrazone. An eventual recovery of 1·86 g. of unchanged trisubstituted hydroxylamine being taken into account, the calculated recovery of acetone derivative is 0·17 g. for the hydrolysis of one *iso*propyl group and 0·35 g. for hydrolysis of both. No tractable products could be isolated from the neutralised hydrolysate.

Reduction of ON-*Di*-(2-*cyano*-2-*propyl*)-N-*phenylhydroxylamine* (IV; Ar = Ph).—3 G. of zinc dust were added slowly to a cold solution of the hydroxylamine (3·0 g.) and powdered anhydrous sodium acetate (0·6 g.) in acetic anhydride (18 c.c.). The mixture was heated gently until it became clear and was then refluxed for not more than 10 min.; a red colour developed. Acetic acid (5 c.c.) was added, the mixture was filtered hot, and the residue washed with a little boiling acetic acid. The total filtrate was, while boiling, treated cautiously with sufficient water to destroy the free acetic anhydride, then cooled in ice-water, made alkaline (10% sodium hydroxide), and extracted with ether. The residue (1·5—2·5 g.) from the dried ether solution was chromatographed through alumina, and from the column there were isolated in the following order azobenzene (0·1 g., m. p. and mixed m. p. 66°), unchanged trisubstituted hydroxylamine, *N*-(2-cyano-2-propyl)-*N*-phenylhydroxylamine (0·3 g.) (VI; Ar = Ph), and acetanilide (0·8 g.).

Reductions of the other trisubstituted hydroxylamines were carried out similarly. From the *o*-chlorophenyl, mesityl, and *p*-tolyl compounds the secondary hydroxylamines could not be obtained even on prolonged heating, though correspondingly more aryl acetamides were then formed. The new reaction *products* are listed in Table 2.

Reduction of N-(2-*Cyano*-2-*propyl*)*aniline*.—This aniline (IX; Ar = Ph) (Bucherer and Grolee, *Ber.*, **1906**, **39**, 986) (2 g.) was dissolved in acetic acid or anhydride (20 c.c.) and zinc dust (2 g.) was added. The mixture was heated for a few minutes under reflux, filtered, made alkaline after cooling, and extracted with ether. On addition of light petroleum (b. p. 20—40°) to the ether solution, acetanilide (0·5 g.) crystallised (m. p. and mixed m. p. 114°).

Reactions of s-*Trinitrobenzene and* 2 : 4-*Dinitrochlorobenzene with* 2-*Cyano*-2-*propyl Radicals*.—In each case, the nitro-compound (0·04 mole) was dissolved in toluene (100 c.c.) with $\alpha\alpha'$-azo*iso*butyronitrile (0·04 mole). After refluxing for 2½ hr., the solution was distilled in steam and from the distillate there was obtained tetramethylsuccinonitrile (75—80%). The nitro-compounds were recovered quantitatively from the residue of the steam-distillation by ether-extraction.

Few infra-red spectra of compounds containing N–O–C or N–O–H bands have been described hitherto, and it was hoped that the data collected in Table 3 would provide evidence for diagnostic characterisation of the N–O link. Aliphatic ethers are known to have rather wide absorption bands between 8 and 9 μ owing to flexing of the covalencies attached to the oxygen atom, whilst tertiary amines have similar bands in the 9—10 μ region.

Our tertiary hydroxylamines $R_1R_2N{\cdot}OR_1$ have at least 4 pronounced and sharply defined bands in the 8—9 μ region, most of which also appear in the secondary hydroxylamines $R_1R_2N{\cdot}OH$. Discrimination between the very similar covalencies of the system $\begin{matrix}C\\C\end{matrix}\!\!>\!N{\cdot}O{\cdot}C$ is difficult, for any movement of the nitrogen atom necessarily affects the bond angles and bond lengths of all the attached groups. Though no definite assignment to these covalencies can be made, we suggest that at least one of the bands regularly occurring in the 8—9 μ region is due to the N–O bond. Grouped bands are also found in the 9·5—11·5 μ region; this wave-length is shorter than those at which characteristic out-of-plane absorptions of aromatic substituents can be observed, and so these bands too can probably be ascribed to bending frequencies associated with the nitrogen or oxygen atoms of the hydroxylamines.

This work has been carried out during the tenure by one of us (B. A. G.) of a Post-doctorate Research Fellowship of the National Research Council of Canada, and subsequently of a Merck Post-doctorate Fellowship of the Merck & Co. Ltd., Montreal, Canada.

The Dyson Perrins Laboratory, Oxford. [*Received, December 17th*, 1953.]

Immunopolysaccharides. Part I. Preliminary Studies of a Polysaccharide from Azotobacter chroococcum, *containing a Uronic Acid.*

By G. J. Lawson and M. Stacey.

[Reprint Order No. 5042.]

The acidic capsular polysaccharide of the soil organism *Azotobacter chroococcum* (Cooper, Daker, and Stacey, *Biochem. J.*, 1938, **32**, 1752) which gives serological cross reactions with certain pneumococcal specific antisera contains principally D-glucose and D-galactose units with a small proportion of D-glucuronic acid residue. From a neutral part of the methylated polysaccharide there were identified 2 : 3 : 6-tri-*O*-methyl-D-glucopyranose, 2 : 4 : 6-tri-*O*-methyl-D-glucopyranose, 2 : 3-di-*O*-methyl-D-glucopyranose, and 2 : 4 : 6-tri-*O*-methyl-D-galactopyranose. From an acidic portion of the hydrolysate there were isolated 2 : 4 : 6-tri-*O*-methylglucose, 2 : 3-di-*O*-methylglucose and 2 : 3-di-*O*-methyl-D-glucuronic acid. Comments on the structure are made. Possession of the aldobiuronic acid component accounts for the cross serological activity.

Following the description by the senior author with other colleagues (Cooper, Daker, and Stacey (*Biochem. J.*, 1938, **32**, 1752) of an acidic polysaccharide produced by *Azotobacter chroococcum*, frequent attempts have been made to elucidate its structure. Although methylated derivatives could readily be made, these on methanolysis gave a very complicated mixture of methylated glycosides which even a most elaborate series of high-vacuum fractionations failed to separate satisfactorily. Chromatographic techniques now make it possible to attack the problem afresh.

The prolific production of capsular material, long recognised as a characteristic of *Azotobacter* species, may be an important factor in the development of humic substances in certain soils. From the recognition of glucose and uronic acids as constituents of the polysaccharide, Cooper, Daker, and Stacey (*loc. cit.*) placed it in the same class of compound as the immunologically specific polysaccharides of various pneumococcal types. Some while ago Professor M. Heidelberger kindly carried out some precipitin experiments for us with the *Azotobacter* polysaccharide and with a polysaccharide from *Rhizobium radicicolum*, with various pneumococcal specific antisera. He showed that both polysaccharides separately gave cross precipitin reactions in high dilution (1 : 100,000 after 4 hours at room temperature) with Type III anti-*Pneumococcus* horse serum and also with a mixture of anti-*Pneumococcus* sera of Types VI and XIV. It has been shown (Schlüchterer and Stacey, *J.*, 1945, 776) that part of the structure for the *Rhizobium* polysaccharide bore a close resemblance to that of the Tvpe-III *Pneumococcus*-specific polysaccharide inasmuch as they both contained cellobiuronic acid residues in their respective repeating units. (In Schlüchterer and Stacey's paper the linkages in the oxycellulose formula are incorrectly shown as α instead of β.) The significance of the cellobiuronic acid unit in relating chemical constitution to serological specificity was demonstrated by Heidelberger and Hobby (*Proc. Nat. Acad. Sci.*, 1948, **28**, 516) in work with Types III and VIII anti-*Pneumococcus* horse sera and various oxycelluloses.

The nature of the uronic acid component of the *Azotobacter* polysaccharide is therefore of interest. It formed, however, a minor component only of the polysaccharide and indeed highly viscous polysaccharides have since been isolated from various other strains of *Azotobacter chroococcum* in which no uronic acid component could be detected.

The sample of material selected for the present study was part of the original sample described by Cooper, Daker, and Stacey (*loc. cit.*), and the crude material was purified by repeated precipitation from aqueous solution by ethyl alcohol. It appeared to be inhomogeneous and was obtained after being dried, as a water-soluble white fibrous solid, nitrogen-free and having a low negative optical activity. The free acid, obtained by repeated precipitation from acid solution, contained only traces of inorganic material. Paper chromatography of an acid hydrolysate revealed the presence of glucose, galactose and

glucuronic acid, the amount of the latter being estimated as *ca.* 4%. An unidentified sugar was also present. The galactose component had not previously been identified.

The polysaccharide was readily methylated satisfactorily by the usual techniques; the methylated polysaccharide was an acid which was carefully fractionated by solvent-precipitation from chloroform solution. An essentially homogeneous fraction (85% yield) was selected for methanolysis by boiling 5% methanolic hydrogen chloride for eight hours. By solvent extraction the hydrolysate was separated into a mixture of methyl glycosides and the barium salt of a partly methylated uronic acid derivative. Further complete methylation of the mixture of glycosides followed by isolation of the resulting tetra-*O*-methylhexoses and fractional crystallisation of their phenylglycosylamines showed it to contain D-glucopyranose and D-galactopyranose residues in the approximate ratio of **3 : 1**.

The glycoside mixture was subjected to a complex series of fractional distillations in a high vacuum. No tetramethylhexose fraction could be detected. The properties of the various fractions and examination of them by paper chromatography indicated that this original mixture consisted of methyl tri-*O*-methylhexosides and methyl di-*O*-methylhexosides. Further methylation and examination of the tetra-*O*-methylhexoses produced, showed that both the tri- and the di-*O*-methylhexosides contained derivatives of both D-glucose and D-galactose. Preparation of crystalline aniline derivatives of the free sugars prepared from the mixture of tri-*O*-methylhexosides indicated the presence of **2 : 4 : 6**-tri-*O*-methyl-D-glucopyranose and **2 : 4 : 6**-tri-*O*-methyl-D-galactopyranose.

Various fractions having essentially similar properties were mixed, hydrolysed, and, initially in collaboration with Dr. J. K. N. Jones, were separated on cellulose columns according to the original method described by Hough, Jones, and Wadman (*J.*, 1949, 2511). The mixed methyl trimethylhexosides were found to consist of **2 : 3 : 6**-tri-*O*-methyl-D-glucopyranose (40%), **2 : 4 : 6**-tri-*O*-methyl-D-glucopyranose (15%), and **2 : 4 : 6**-tri-*O*-methyl-D-galactopyranose (15%), together with unidentified material.

The fractions with lower methoxyl content contained small amounts of the same three trimethyl sugars together with two dimethylhexoses one of which was identified as **2 : 3**-di-*O*-methyl-D-glucopyranose.

The barium salt, which gave a strong naphtharesorcinol test for uronic acid, had the properties of an oligosaccharide derivative and was further hydrolysed with 2N-sulphuric acid. After neutralisation and removal of barium ions with a resin the mixture of free sugars was fractionated on a cellulose column. There were separated **2 : 4 : 6**-tri-*O*-methyl-D-glucose (30%), **2 : 3**-di-*O*-methyl-D-glucose (30%), and a di-*O*-methyl-D-glucuronic acid containing the **2 : 3**-di-*O*-methyl derivative. At this stage of the work it is not possible to estimate the molecular structure of the polysaccharide but several important facts have been established. The absence of a fully methylated "end" group and the significant content of dimethylhexoses indicate that the molecule is a highly branched structure similar to that of the serologically related *Rhizobium radicicolum* polysaccharide. The main chain of the polysaccharide is built up from both glucose and galactose residues in the proportion of **3 : 1**. From the direction of rotational change on hydrolysis of the polysaccharide and on methanolysis of its methyl ether and from the infra-red spectrum of the parent polysaccharide (Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171) it is clear that the linkages were mainly of the β-type. The galactose residues and a proportion of the glucose residues are linked through the **1** and the **3** position. Other glucose residues are attached by both the **1** ⟶ **4** and the **1** ⟶ **6** linkages. The order of attachment of the hexose residues has not yet been established but it is clear that glucose units form the main branch points in the molecule.

The most striking finding is that only glucose residues are isolated from the glucuronic acid-containing oligosaccharide. In this portion of the molecule the proved **1** ⟶ **3** linkages of the glucose units and the **1** ⟶ **4** linkages in the glucuronic acid residue, together with the glucose residues with undoubted β-linkages in the molecule show a very close structural relation to that of the Type-III *Pneumococcus* specific polysaccharide molecule (Reeves and Goebel, *J. Biol. Chem.*, 1941, **131**, 511). This structural similarity undoubtedly accounts for the Type III cross serological relationships already mentioned.

Experimental

Properties of the Polysaccharide.—The polysaccharide was part of the material prepared on a gelatine medium by the method of Cooper, Daker, and Stacey (*loc. cit.*), and it contained a high proportion of ash and a protein constituent (total N, 1·0%). It was purified by repeated precipitation from dilute hydrochloric acid solution by addition of alcohol and when dried it formed an asbetos-like mass which was essentially free from ash and nitrogen and had $[\alpha]_D^{15}$ −10°.

Infra-red Absorption Spectra.—The infra-red spectra of both the *Azotobacter* polysaccharide and the *Rhizobium radicicolum* polysaccharide were investigated in the range 1700—725 cm.$^{-1}$. The absence of absorption at 840 cm.$^{-1}$ in the case of both polysaccharides and the presence of peaks of moderate intensity at 890 cm.$^{-1}$ and 892 cm.$^{-1}$ in the case of the *Azotobacter* and *Rhizobium* polysaccharides, respectively, indicate that in each case the glucose units in the polysaccharides, are in the β-configuration.

The presence of absorption peaks at 1595 and 1583 cm.$^{-1}$ in the spectrum of the *Rhizobium* polysaccharide confirmed the presence of the carboxylate ion arising from the glucuronic acid residues. Relatively weak absorption was displayed in the same region by the *Azotobacter* polysaccharide showing that the proportion of uronic acid residues in this polysaccharide was very small.

Hydrolysis and Chromatographic Behaviour.—A sample of the polysaccharide (40 mg.) was hydrolysed at 100° for 2 hr. with 2N-sulphuric acid (10 c.c.). After being neutralised with barium carbonate the hydrolysate was analysed (*a*) by separation for 1—3 days in butyl alcohol (40%)–ethyl alcohol (10%)–water (49%)–ammonia (1%) by ordinary paper chromatography and the components present detected by spraying with aniline hydrogen phthalate, (*b*) by ionophoresis in a borate buffer (pH 10·6) for 1—2 hr. at 900 v and the components detected by spraying with aniline hydrogen phthalate. The sugars identified were glucose (major portion), galactose (minor portion), glucuronic acid (trace), and mannose (trace).

In addition an unidentified sugar was present in significant amount. It stained yellowish-brown with aniline hydrogen phthalate and had a high R_F value (>0·5) and a negligible *Mg* value. It would appear to be a dideoxy-sugar and it is still under investigation.

Methylation Procedure.—The polysaccharide (15 g.) (ash, 5%; moisture, 24%) in water (100 c.c.) and 30% aqueous sodium hydroxide (80 c.c.), was stirred at room temperature for 2½ hr. during the dropwise addition of 30% sodium hydroxide (10 × 40 c.c.) and dimethyl sulphate (11 × 16 c.c.). After a further 3 hours' stirring, the mixture was heated at 100° for 10 min., cooled in ice, and neutralised (5N-sulphuric acid). When reheated to 100°, the separated sodium sulphate redissolved, and the insoluble methyl ether was filtered off. Partially methylated material remaining in the filtrate was recovered by cooling, removing the sodium sulphate, and concentrating the liquor to dryness at 30°, the residue being added to the bulk of the methylated product and further methylated at 16°. Four more methylations were applied. The crude product, separated as the sodium salt, was purified by suspending it in water (200 c.c.), acidifying it (Congo-red) with sulphuric acid, and shaking it with equal volumes of chloroform–acetone (5 : 1). The resulting solution was washed, dried, and concentrated, and the acidic methylated product precipitated by addition of excess of light petroleum (b. p. 40—60°). A sample so isolated after four methylations had: ash, 1·2; OMe (corr.), 37·0%: after six methylations the product, after being dried in a vacuum, formed a white powder (6·94 g.): ash, 0·4; OMe (corr.), 40·0%. Further methylation did not increase the methoxyl content.

Fractionation of the Methylated Polysaccharide.—The methylated polysaccharide (6·8 g.) was dissolved in chloroform (100 c.c.)–acetone (25 c.c.) and fractionally precipitated by the gradual addition of light petroleum (b. p. 40—60°). The precipitates were isolated on the centrifuge, washed with petroleum, and dried in a vacuum at 60°. Fractions were obtained as follows:

Fraction	Wt. (g.)	Ash (%)	OMe (%)	$[\alpha]_D^{21}$	n_D^{25}
F1	0·22	—	—	—	—
F2	3·905	0·3	38·5	−24°	3·78
F3	0·739	nil	38·8	−25	1·80
F4	0·308	nil	39·5	−25	0·79
F5	1·114	nil	40·5	+27	0·35
F6	0·099	nil	—	—	—

[All rotations and viscosities were measured at 0·9% concentration in chloroform–acetone (8 : 1).]

Fractions F1, which was mainly inorganic, and F6, a syrup obtained by evaporation of the final liquors, were not investigated. F2 separated very rapidly as a gel, which hardened when ground with light petroleum (b. p. 40—60°). Attempts to re-fractionate F2 succeeded in

separating only traces of material with reduced viscosity, the bulk remaining unchanged. Fractions F2 and F3 gave identical hydrolysis curves and thus were reasonably homogeneous. They were therefore combined for methanolysis with similar fractions from subsequent methylations and fractionations: F4 was not further investigated.

Fraction F5 was relatively unstable to acid: when boiled with 0·25% dry methanolic hydrogen chloride, its rotation changed: $[\alpha]_D$ +27° (initial), +66° (15 min.), +66° (30 min.), +62° (45 min.), +61° (90 min.), +54° (210 min.), +49° (330 min.), +44° (510 min., equilibrium value). It was not further investigated.

Esterification of the Methylated Polysaccharide.—Fraction F2 (80·3 mg.), dissolved in dry methanol (10 ml.), was treated with an excess of ethereal diazomethane, slight effervescence occurring. After removal of the solvents, the residue was dissolved in chloroform–acetone (8 : 1) and precipitated by addition of light petroleum, forming a white powder {ash, 0·6; OMe (corr.), 39·3%; $[\alpha]_D^{20}$ −25°; $n_{sp.}^{25}$ 1·82}.

Methanolysis of the Methylated Polysaccharide.—Preliminary experiments showed that the most convenient concentration of methanolic hydrogen chloride was 5%. The methylated polysaccharide (10·0 g.) was boiled under reflux with 5% dry methanolic hydrogen chloride (500 c.c.). The polysaccharide was treated in batches in order to compare the methanolysis curves of various fractions: typical rotations were as follows: $[\alpha]_D$ +6° (1 hr.), +26·5° (2 hr.), +47·5° (3·5 hr.), +56·5° (4·5 hr.), +65·5° (6 hr.), +70·5° (7 hr.), +77·5° (9 hr.), +81·5° (11 hr.), +88° (14 hr.), +90·5° (17 hr.), +92° (19 hr.), +94° (22 hr.), +94·5° (24 hr.), +95° (27 hr., equilibrium value). The combined mixtures, after neutralisation with silver carbonate, were filtered, the silver residues well washed with warm methanol, and the combined filtrate and washings concentrated to a syrup. This syrup, which did not reduce Fehling's solution, was digested for 3½ hr. at 50—60° with saturated aqueous barium hydroxide (200 c.c.), the solution neutralised with carbon dioxide and filtered, and the barium carbonate exhaustively extracted with methanol. The combined aqueous and methanolic solutions were evaporated at 40—50° to a syrup which after being dried in a vacuum (P_2O_5) was dissolved in dry methanol (20 c.c.), and dry ether (50 c.c.) added. Addition of dry light petroleum precipitated a barium salt which was isolated on the centrifuge, twice reprecipitated from the same solvents, and finally triturated with ether. "Barium salt (A1)" formed a white powder (0·911 g.) giving a positive naphtharesorcinol test. The equiv. weight was estimated by dissolving it in an excess of ethanolic hydrogen chloride, and back titrating potentiometrically [Found: OMe, 29·9; Ba (sulphated ash), 5·8%; equiv., 496].

The liquors and washings from the separation of the barium salt were concentrated to a syrup, "Glycosides A1" (9·030 g.), which gave a negative naphtharesorcinol test {Found: OMe, 29·9%; $[\alpha]_D^{20}$ +76·5°, *c*, 1·9 in $CHCl_3$}.

Methylation of "Glycosides A1".—"Glycosides A1" (0·486 g.) was methylated four times with methyl iodide and silver oxide, and the resulting syrup (0·503 g.) distilled in a high vacuum, as follows:

Fraction	Wt. (g.)	B. p./0·005 mm.	n_D^{19}	OMe (%)	Physical state
GT1	0·275	62—69°	1·4440	62·0	Highly mobile syrup
GT2	0·039	Bath temp. 200	1·4568	—	Mobile syrup
GT3	0·189	Still residue	—	—	Dark resin

Fraction GT1 (0·25 g.), which showed $[\alpha]_D^{20}$ +94° in chloroform (*c*, 1·0), was hydrolysed at 100° with 1·5N-sulphuric acid (20 c.c.): $[\alpha]_D^{18}$ +106·5° (initial) ⟶ +80° (19·5 hr., equilibrium value). The strongly-reducing hydrolysate was neutralised (litmus) with sodium hydroxide, evaporated to dryness at 40°, and the dry residue extracted with chloroform. The filtered extract was concentrated to a syrup which crystallised; repeated recrystallisation from light petroleum (b. p. 60—80°) afforded needles (0·058 g.) of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, m. p. and mixed m. p. 80—86°, $[\alpha]_D^{26}$ +84° (*c*, 1·0 in H_2O) (Found: OMe, 52·3. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The sugar (0·1 g.) was slowly distilled with aniline (0·04 g.), in dry ethanol (2 c.c.) and dry benzene (0·5 c.c.) during 7 hr. After removal of solvents crystalline tetra-*O*-methyl-*N*-phenylglucopyranosylamine was obtained, having m. p. and mixed m. p. 131—133°.

The mother-liquors from which the crystalline hexose had been isolated were concentrated to a syrup (0·126 g.) which was similarly converted into the aniline derivative. The resulting syrup was dissolved in a little hot ethanol, needles (23 mg.) separating on cooling. They were tetra-*O*-methyl-*N*-phenyl-D-galactopyranosylamine, m. p. and mixed m. p. 191°, $[\alpha]_D^{17}$ −68° ⟶ +41° (*c*, 0·4 in $COMe_2$). Concentration of the ethanolic mother-liquors afforded a residue which when crystallised from light petroleum yielded needles (10 mg.) of the above aniline derivative of tetra-*O*-methyl-D-glucose.

Distillation of "Glycosides A1."—"Glycosides A1" (8·536 g.) was distilled in a high vacuum from a Widmer flask, as follows:

Fraction	Wt. (g.)	B. p./0·005 mm.	n_D^{18}	OMe (%)	$[\alpha]_D^{20°}$ in $CHCl_3$	Physical state
M1	3·700	90—94°	1·4587	51·6	+88° (*c*, 1·1)	Mobile syrup
M2	0·769	100—120	1·4619	49·5	+95° (*c*, 2·2)	Syrup
M3	3·930	—	—	—	—	Very viscous brown syrup

The first drop of distillate had n_D^{18} 1·4579, indicating the absence of any tetra-*O*-methylhexosides.

Fraction M3 was further hydrolysed by boiling 10% methanolic hydrogen chloride as follows: $[\alpha]_D$ +76·5° (1·0 hr.), +80·5° (3·0 hr.), +87·5° (7·5 hr.), +88·5° (10·5 hr.), +90·5° (13·5 hr., equilibrium value). The hydrolysate, non-reducing and giving a negative naphtharesorcinol test, was neutralised with silver carbonate and worked up in the usual way to yield a syrup, "Glycosides A2," having OMe, 37·2%. Treatment with barium hydroxide failed to yield a barium salt, thereby confirming the absence of any uronic acid residues.

Distillation of "Glycosides A2." This syrup (3·722 g.) was distilled from a Widmer flask as follows:

Fraction	Wt. (g.)	B. p./0·005 mm.	n_D^{19}	OMe (%)	$[\alpha]_D^{20}$ in $CHCl_3$	Physical state
M3*a*	0·951	104—120°	1·4596	50·0	+99° (*c*, 2·1)	Syrup
M4	0·973	124—125	1·4685	44·8	+93° (*c*, 1·0)	Viscous syrup
M5	1·690	residue	—	—	—	Brown resin

Redistillation of fraction M5 produced one fraction (0·295 g.), b. p. 120—180°/0·007 mm., n_D^{18} 1·482 (Found: OMe, 36·1%), which formed a gel on cooling. Since these properties did not correspond with those of a monosaccharide derivative, the distillate was recombined with the residue and boiled under reflux with 10% methanolic hydrogen chloride for 52 hr., the solution being too dark for optical measurements. From the hydrolysate syrupy "Glycosides A3" (1·422 g.; OMe, 36·0%) was obtained in the usual way and distilled:

Fraction	Wt. (g.)	B. p./0·005 mm.	n_D^{21}	OMe (%)	$[\alpha]_D^{20}$ in $CHCl_3$	Physical state
M6	0·212	106—110°	1·4612	44·8	+77° (*c*, 1·1)	Mobile syrup
M7	0·287	111—118	1·4740	43·5	+84·5° (*c*, 1·0)	Syrup
M8	0·145	131—*ca.* 200	1·472	40·0	+88° (*c*, 1·0)	Slightly yellow viscous syrup
M9	0·712	residue	—	36·5	—	Dark resin

The residue was not investigated.

Preliminary Chromatographic Examination of Fractions M1—M9.—Small portions of these glycoside fractions were hydrolysed for 30 min. with boiling 2·5N-sulphuric acid, the hydrolysate being neutralised with sodium hydroxide and evaporated to dryness. The residue was extracted with chloroform, evaporation of each extract yielding a reducing syrup which was dissolved in a few drops of water. A little of each solution was placed at the top of a Whatman No. 1 filter-paper chromatogram (45 × 10 cm.) and allowed to dry, and the paper irrigated for 12 hr. with the organic phase of an acetic acid–*n*-butanol–water mixture (1 : 4 : 5). After being dried and developed in the usual way with ammoniacal silver nitrate, each fraction was found to give two spots, corresponding to a trimethyl- and a dimethyl-hexose, their relative intensities varying roughly according to the methoxyl content of the original hexoside fraction. No evidence was obtained of any spot corresponding to a tetra-*O*-methylhexose. Applied to known methylated hexoses, the above procedure clearly separated di-, tri-, and tetra-methylglucose, but failed to give adequate separation between the isomeric trimethylglucoses. Fractions M2 and M3 gave identical chromatograms, and were combined for further examination.

Hydrolysis of Fraction M1. Fraction M1 (1·01 g.) was hydrolysed with 1·5N-sulphuric acid (50 c.c.) at 100°: $[\alpha]_D^{18}$ +103° (0·25 hr.) ⟶ +72° (17 hr., equilibrium value). The strongly-reducing hydrolysate was neutralised with sodium hydroxide and worked up as previously described, yielding syrup (0·939 g.; OMe, 41·5%). A portion (0·205 g.) was converted into the aniline derivative (50 mg.), identified as the derivative of 2 : 4 : 6-tri-*O*-methyl-D-glucose.

Methylation of Fraction M1.—Fraction M1 (0·977 g.) was methylated four times with methyl iodide and silver oxide, and the resulting syrup (1·033 g.; OMe, 58·6%) distilled in a high vacuum as follows:

Fraction	Wt. (g.)	B. p./0·02 mm.	$n_D^{19·5}$	(OMe %)	$[\alpha]_D^{18}$ in $CHCl_3$	Physical state
M1T1	0·864	64°	1·4438	62·4	+94° (*c*, 1·0)	Highly mobile syrup
M1T2	0·100	130	1·4469	56·4	+98° (*c*, 1·0)	Mobile syrup
M1T3	0·059	residue	—	—	—	Brown resin

M1T2 and M1T3 were not investigated.

Hydrolysis of Fraction M1T1.—This fraction (0·84 g.) was hydrolysed with 1·5N-sulphuric acid at 100°, the following rotations being obtained: $[\alpha]_D^{18}$ +106° ⟶ +87° (17 hr., equilibrium value). When worked up in the usual way, the strongly-reducing hydrolysate afforded a syrup (0·782 g.) which partially crystallised as needles (0·120 g.), m. p. 77—81° alone and in admixture with tetra-*O*-methyl-D-glucopyranose, $[\alpha]_D^{19}$ +87° (*c*, 1·0 in H_2O) (Found: OMe, 52·6. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The free sugar (0·110 g.) was converted into the aniline derivative, which formed needles (0·035 g.) (from ethanol), m. p. 133—134° unchanged in admixture with the aniline derivative of tetra-*O*-methyl-D-glucose, $[\alpha]_D^{18}$ +240° (*c*, 1·0 in $COMe_2$) (Found: OMe, 39·8. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9%).

The mother-liquors from the isolation of the free sugar were concentrated to a syrup (0·503 g.) which was converted into the aniline derivative. Repeatedly crystallised from ethanol, the product formed needles (0·053 g.), m. p. 192—193°, of the aniline derivative of tetra-*O*-methyl-D-galactopyranose, $[\alpha]_D^{17}$ −80° ⟶ +44° (*c*, 0·50 in COMe) (Found: OMe, 39·7. Calc. for $C_{16}H_{25}O_5N$: OMe, 39·9%). No glucose derivatives could be isolated from the mother-liquors.

Hydrolysis of Fractions M2 and M3.—The combined fractions (0·872 g.) were hydrolysed by 1·5N-sulphuric acid at 100°: $[\alpha]_D^{18}$ +104° ⟶ +66·5° (19·5 hr., equilibrium value). The usual procedure yielded a strongly-reducing syrup (0·827 g.; OMe, 35·6%). A portion (0·400 g.) was converted into the aniline derivative, which was a mixture, white needles (21 mg.), m. p. 155° after sintering at 150°, $[\alpha]_D^{18}$ −93° ⟶ +86° (*c*, 0·25 in $COMe_2$).

Methylation of the Combined Fraction M2—M3.—The combined fraction (0·737 g.) was methylated six times with methyl iodide and silver oxide, and the resulting syrup (0·734 g.; OMe, 59·1%) distilled in a high vacuum as follows:

Fraction	Wt. (g.)	B. p./0·005 mm.	n_D^{20}	OMe (%)	$[\alpha]_D^{20}$ in $CHCl_3$	Physical state
M2T1	0·568	67°	1·4430	61·7	+100° (*c*, 1·0)	Highly mobile syrup
M2T2	0·092	100	1·4550	54·3	+95·5° (*c*, 1·0)	Mobile syrup
M2T3	0·047	residue	—	—	—	Brown resin

M2T2 and M2T3 were not investigated.

Fraction M2T1 (0·56 g.) was hydrolysed at 100° with 1·5N-sulphuric acid: $[\alpha]_D^{18}$ +109° ⟶ +79·5° (15·5 hr., equilibrium value). The usual isolation procedure afforded a strongly-reducing syrup (0·471 g.) which partially crystallised. The crystals were separated by trituration with ether and filtration: repeatedly recrystallised from dry ether–dry light petroleum (b. p. 60—80°) they formed needles (0·068 g.) of tetra-*O*-methyl-D-glucopyranose (aniline derivative, m. p. 136°).

The mother-liquors from the isolation of the sugar were evaporated to a syrup (0·228 g.) which was converted into the aniline derivative, identified as that of tetra-*O*-methyl-D-glucopyranose.

Separation of Hexoside Mixtures on Cellulose Columns.—Samples of the free sugars obtained by hydrolysis of fractions M1 and the combined M2—M3 were combined (total wt., 1·21 g.), dissolved in *n*-butanol–light petroleum (b. p. 80—100°), and separated on cellulose by the method of Hough, Jones, and Wadman (*loc. cit.*), yielding 6 fractions. The first two (0·55 g. and 0·12 g.) consisted mainly of a sugar with R_G value 0·83 together with a trace of a sugar with R_G 0·76. The syrup slowly crystallised, recrystallisation from ether affording 2 : 3 : 6-tri-*O*-methyl-D-glucose, R_G 0·83, m. p. 116° alone and in admixture with an authentic specimen.

Three sugars, R_G values 0·83, 0·76, and 0·68, were present in the remaining four fractions, which were as follows:

Fraction	3	4	5	6
Wt. (g.)	0·08	0·07	0·16	0·28
$[\alpha]_D$ in water	+60°	—	+61°	+70°

Fraction 3 partially crystallised and was identified as 2 : 4 : 6-trimethylglucose. The residue was converted into the aniline derivative in the usual way, the product after recrystallisation from ethanol–ether having m. p. 164°, alone and mixed with the aniline derivative of 2 : 4 : 6-tri-*O*-methyl-D-glucose. The free sugar from this anilide had R_G 0·77, identical with 2 : 4 : 6-tri-*O*-methyl-D-glucose.

The last three fractions did not crystallise: the largest (fraction 6) was converted into the aniline derivative, yielding a product which after recrystallisation from ethanol had m. p. 177°, undepressed on admixture with the authentic aniline derivative of 2 : 4 : 6-tri-*O*-methyl-D-galactose (m. p. 178°). The free sugar had R_G 0·68: 2 : 4 : 6-tri-*O*-methyl-D-galactose has R_G 0·67.

Examination of "Barium Salt A1."—"Barium salt A1" (0·67 g.) was hydrolysed with boiling 2N-sulphuric acid (60 c.c.) for 5 hr. ($[\alpha]_D^{16}$ *ca.* +50°, equilibrium value); the hydrolysate was neutralised with barium carbonate and filtered. The filtrate was treated with Amberlite resin (IR-100) and concentrated to a syrup (0·4 g.) which was found by paper chromatography to contain two sugars. These were separated on a cellulose column, water-saturated *n*-butanol being used as developing solution, whereby three fractions were obtained. The first on concentration afforded crystalline 2 : 4 : 6-tri-*O*-methyl-D-glucose (0·11 g.), m. p. 123° alone and mixed with an authentic sample. The third fraction (0·1 g.) consisted of a dimethylhexose: this was shown to be a glucose derivative by methylation with silver oxide and methyl iodide, the product on hydrolysis affording crystalline 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, m. p. and mixed m. p. 94°, and was identified in a separate experiment as 2 : 3-di-*O*-methyl-D-glucose. The intermediate fraction (0·17 g.) contained largely a mixture of 2 : 4 : 6-tri-*O*-methyl-D-glucose and 2 : 3-di-*O*-methyl-D-glucose. No galactose derivative could be detected in this fraction and the uronic acid derivative was not identified.

Another sample of "Barium salt A1" (0·5 g.) was hydrolysed as above, neutralised with barium carbonate, and evaporated to dryness. The solid was exhaustively extracted in a Soxhlet extractor with chloroform–acetone to remove the methylated sugars. The residue was dissolved in 10 c.c. of water, a few drops of bromine added, and the solution kept at room temperature for 24 hr. After evaporation of the water and extraction of the dry residue with ether there was obtained from the ethereal solution a syrup (50 mg.), which was boiled with dry 1% methyl alcoholic hydrogen chloride (5 c.c.). After removal of the hydrochloric acid with silver carbonate the filtered solution was saturated with ammonia and kept overnight. Removal of the solvent gave a crystalline product (20 mg.), identified by m. p. and mixed m. p. 156° as 2 : 3-di-*O*-methyl-D-glucarodiamide (Smith, *J.*, 1940, 1045).

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*The Catalytic Cyclic Polymerisation of Butadiene.**

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The dimerisation of butadiene to *cyclo*octa-1 : 5-diene is catalysed by bistriphenylphosphinedicarbonylnickel^0 in the presence of acetylene. Complexes of nickel carbonyl with trimethyl or triphenyl phosphite catalyse the dimerisation without added acetylene, but are more active in the presence of acetylene. Trimers and tetramers of butadiene are also formed, consisting in part of compounds containing 12- and 16-membered rings, respectively. Small amounts of compounds formed from both butadiene and acetylene have been detected.

THE remarkable ability of certain complexes derived from nickel carbonyl to polymerise acetylenic compounds to aromatic compounds was described by Reppe and Schweckendiek (*Annalen*, 1948, **560**, 104). In particular, the disubstituted complex bistriphenylphosphinedicarbonylnickel^0 $(Ph_3P)_2Ni(CO)_2$ catalysed the polymerisation of acetylene to benzene and styrene under extremely mild conditions, and of propargyl alcohol which similarly led to a mixture of 1 : 2 : 4- and 1 : 3 : 5-trishydroxymethylbenzene. Further examples of this catalytic trimerisation of ethynyl compounds have been provided by Rose and Statham (*J.*, 1950, 69) and by McKeever and Van Hook (U.S.P. 2,542,551); one case of the successful polymerisation of a disubstituted acetylene, but-2-yn-1 : 4-diol, is recorded by

* Part of this work has been described in B.P. 701,106 and B.P. Appl. 27,070/51, and was read at a Chemical Society symposium on February 5th, 1953 (*Chem. and Ind.*, 1953, 239).

Kleinschmidt (U.S.P. 2,542,417) who obtained hexahydroxymethylbenzene by using the monosubstituted complex $(Ph_3P)Ni(CO)_3$.

Reppe and Schweckendiek also claimed that complexes of triphenylphosphine with certain metal halides, *e.g.*, $(Ph_3P)_2NiBr_2$ and $(Ph_3P)_2CuCl$, in addition to the nickel carbonyl complexes, catalysed the polymerisation of vinyl compounds, with or without acetylene, to give derivatives of dihydro-, tetrahydro-, or hexahydro-benzenes. More recently, however, acetylene has been found to react with acrylonitrile and methyl acrylate in the presence of $(Ph_3P)_2Ni(CO)_2$ to give the open-chain compounds 1-cyanohexa-1 : 3 : 5-triene and methyl hepta-2 : 4 : 6-trienoate, respectively (Cairns, Engelhardt, Jackson, Kalb, and Sauer, Abstr. Papers presented at the 120th Meeting Amer. Chem. Soc., Sept. 1951, p. 14M; *J. Amer. Chem. Soc.*, 1952, **74**, 5636; Kalb and Sauer, U.S.P. 2,540,736).

A new cyclic polymerisation catalysed by substituted nickel carbonyls has now been discovered. An attempt was made to prepare *cyclo*hexa-1 : 4-diene by Diels–Alder addition of acetylene to buta-1 : 3-diene in the presence of $(Ph_3P)_2Ni(CO)_2$ as catalyst. From the products of reaction in benzene solution at 120°, two readily distillable compounds were obtained. The minor fraction was identified as 4-vinyl*cyclo*hex-1-ene, the normal product of thermal dimerisation of butadiene (see Reed, *J.*, 1951, 685). The chief product, amounting to from three to four times the quantity of vinyl*cyclo*hexene, was substantially pure *cis-cis-cyclo*octa-1 : 5-diene. In further experiments *cyclo*octadiene was obtained in 30—40% yields with about 10% yields of vinyl*cyclo*hexene at butadiene conversions of 50—70% in a reaction time of 4 hr. It was established by infra-red examination of samples of the recovered solvent after careful fractional distillation that no *cyclo*hexa-1 : 4-diene (b. p. 89°; Wooster, U.S.P. 2,182,242) was formed in the reaction.

*cyclo*Octa-1 : 5-diene has been recognised as a by-product of the non-catalytic thermal dimerisation of butadiene (Foster and Schreiber, *J. Amer. Chem. Soc.*, 1948, **70**, 2303; Ziegler, *Angew. Chem., A*, 1947, **59**, 177), forming an increasing proportion of the dimer fraction as the temperature is increased, *e.g.*, 2·2% at 120° to 10·6% at 270°, although the yield of dimer relative to high polymer simultaneously falls from 93% to 57% (Ziegler and Wilms, *Annalen*, 1950, **567**, 1, see also Hillyer and Smith, *Ind. Eng. Chem.*, 1953, **45**, 1133). Reduction of the eight-membered ring dimer of 2-chlorobutadiene, 1 : 6-dichloro-*cyclo*octa-1 : 5-diene (Brown, Rose, and Simonsen, *J.*, 1944, 101; Cope and Schmitz, *J. Amer. Chem. Soc.*, 1950, **72**, 3056), with sodium in liquid ammonia also gives *cyclo*octa-1 : 5-diene (Cope and Bailey, *ibid.*, 1948, **70**, 2305; Cope, Stevens, and Hochstein, *ibid.*, 1950, **72**, 2510) but the overall yield is only 9·6% in a tedious preparation.

The *cyclo*octadiene prepared by this catalytic method was identical with previous preparations, as shown by the close similarity of its Raman spectrum with that reported by Goubeau (*Annalen*, 1950, **567**, 214) for Ziegler and Wilms's compound, the preparation of the crystalline silver nitrate adduct described by Cope, Stevens, and Hochstein (*loc. cit.*), and the formation of only succinic acid by ozonolysis. The compound readily gave *cyclo*octene on semi-hydrogenation but was best characterised by formation of a mono-adduct with 2 : 4-dinitrobenzenesulphenyl chloride (see Kharasch and Buess, *J. Amer. Chem. Soc.*, 1949, **71**, 2724). The diene contained, however, a small amount of an impurity that could not be removed by fractionation. This was indicated by the slightly higher refractive index and lower m. p. than were obtained by previous workers, and by absorption in the infra-red at 765 cm.$^{-1}$ which could not be eliminated completely even by purification of the diene through the silver nitrate adduct. On hydrogenation, a sample of the diene, n_D^{20} 1·4950, absorbed 2·09 mols. of hydrogen to give *cyclo*octane of m. p. 11°, indicating 98·5% purity (Cope and Hochstein, *ibid.*, 1950, **72**, 2515). The possible nature of the impurity is discussed later.

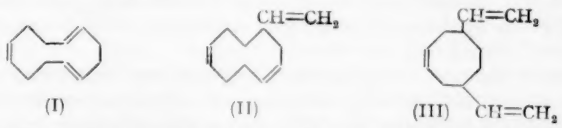
The conditions governing formation of *cyclo*octadiene in this catalytic reaction were examined in some detail. Experiment showed that the phosphine–carbonyl complex was inactive in the absence of acetylene, at least at temperatures below 130°, and the complex was recovered unchanged. At temperatures above 130°, extensive formation of vinyl*cyclo*hexene occurs by purely thermal dimerisation, and catalytic activity leading to *cyclo*octadiene was therefore generally sought in the range 100—120°, at which temperatures the thermal dimerisation of butadiene in solution was shown to be practically negligible.

It follows that the vinyl*cyclo*hexene produced in the catalytic reaction is itself formed catalytically. No *cyclo*octadiene was formed in experiments in which the acetylene was replaced by other ethynyl compounds.

The reaction was extremely sensitive to poisons, the nature of which still remains obscure; extreme cleanliness was absolutely essential for a successful preparation. A decline in yield of *cyclo*octadiene was found in successive runs starting with a clean (sand-blasted) autoclave and new free-space packing until finally it was difficult even to achieve the normal initial catalyst promotion with acetylene and no dimers were formed at all. The use of a glass-lined autoclave partly overcame this poisoning effect, besides facilitating experimental manipulation, but it was not invariably effective. Traces of water and formaldehyde completely inhibit the *cyclo*octatetraene reaction (McKinley, *Ind. Eng. Chem.*, 1952, **44**, 995; Canale and Kincaid, U.S.P. 2,613,231), and in the present reaction it was desirable to add a little calcium carbide to the reaction mixture to ensure complete dryness. Small quantities of other drying agents such as alumina and silica gel appeared to inhibit the reaction, and ethylene oxide and phosphoric oxide gave very much reduced yields of *cyclo*octadiene.

Care was taken to exclude oxygen by repeated purging with nitrogen. Experiments showed that whereas the thermal decomposition of $(Ph_3P)_2Ni(CO)_2$ to triphenylphosphine, nickel, and carbon monoxide was comparatively slow at 140° in boiling xylene in an inert atmosphere, a markedly more rapid decomposition occurred in the presence of oxygen, giving triphenylphosphine oxide. Under comparable conditions, triphenylphosphine was only slowly oxidised to the oxide, showing that the complex itself was attacked directly by oxygen. In an attempt to inhibit polymerisation of the butadiene to high polymer, a small quantity of an antioxidant (generally 2 : 5-di-*tert.*-butyl-1 : 4-benzoquinone) was added to the reaction mixture, but the remarkably beneficial results recorded for similar additions of antioxidants to *cyclo*octatetraene preparations (Barnes, U.S.P. 2,579,106) were not observed. The usual solvent was benzene, but toluene, acetonitrile, *cyclo*hexane, and tetrahydrofuran gave comparable results. The erratic results obtained in this reaction parallel similar experiences recorded in the polymerisation of acetylene to *cyclo*octatetraene (see Copenhaver and Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publ. Corp., New York, 1949, p. 189).

This synthesis of *cyclo*octadiene led to the accumulation of a quantity of a dark brown oil remaining after the removal of the dimers from the reaction products. Distillation of the oil gave an intense blue liquid, b. p. 105—115°/20 mm., from which a fraction, b. p. 113°/120 mm., n_D^{20} 1·5111, analysing as a butadiene trimer, $C_{12}H_{18}$, was obtained on re-distillation. This fraction amounted to about 5% of the *cyclo*octadiene. Hydrogenation showed the presence of three double bonds and hence a monocyclic ring structure. The hydrogenated trimer partly crystallised, yielding 30—35% of *cyclo*dodecane (Ruzicka, Plattner, and Wild, *Helv. Chem. Acta*, 1946, **29**, 1611). This result establishes the formation from butadiene of a twelve-membered ring trimer, presumably the symmetrical *cyclo*dodeca-1 : 5 : 9-triene (I). Distillation of the liquid part of the hydrogenated trimer gave a substance, b. p. 100—110°/14 mm., n_D^{20} 1·4708—1·4829, mainly 1·473—1·479. This



(I) (II) (III)

high refractive index strongly suggests the presence of isomers of *cyclo*dodecane containing other large ring structures, probably ethyl*cyclo*decane derived from the trimer 8-vinyl-*cyclo*deca-1 : 5-diene (II) and diethyl*cyclo*octane isomers derived from corresponding divinyl*cyclo*octenes [*e.g.* (III)]. An attempt to synthesise ethyl*cyclo*decane was unsuccessful since *cyclo*decanone on treatment with ethyl-lithium gave solely the lithium salt of the enol of the ketone. A tendency of ketones of medium ring size to react in this way was observed with *cyclo*octanone (Cope and Fenton, *J. Amer. Chem. Soc.*, 1951, **73**, 1195), and appears to become complete with the ten-membered ring homologue.

It was established that no octahydrodiphenyl, obtained in low yield by Alder and Rickert (*Ber.*, 1938, **71**, 372) by heating vinyl*cyclo*hexene and butadiene, was present by comparison of the infra-red spectrum of the hydrogenated trimer with that of di*cyclo*hexyl.

The formation of these monocyclic butadiene trimers of medium ring size was surprising, especially as nine- to twelve-membered rings have always been the most difficult to prepare (for review, see Prelog, *J.*, 1950, 420). Moreover, although Reppe, Schlichting, and Meister (*Annalen*, 1948, **560**, 93) originally believed that the $C_{10}H_{10}$ and $C_{12}H_{12}$ hydrocarbons formed during the polymerisation of acetylene to *cyclo*octatetraene contained ten- and twelve-membered rings respectively, recent work (Craig and Larrabee, *J. Amer. Chem. Soc.*, 1951, **73**, 1191; Cope and Fenton, *loc. cit.*; Withey, *J.*, 1952, 1930) has shown that it is most unlikely that compounds with rings greater than eight-membered are formed in the reaction.

The compound responsible for the blue coloration of the trimer became concentrated in the later fractions on redistillation, making it probable that the compound is a substituted azulene. This is supported by its stability in air and by ultra-violet analysis, although the concentration of the compound was too low to allow a definite conclusion.

Nickel carbonyl and the fully substituted derivative $Ni(PCl_3)_4$ (Wilkinson, *Nature*, 1951, **165**, 514) were inactive in the reaction. Triphenylphosphine, although readily available to the original German investigators (see B.I.O.S. Surveys Report No. 32, H.M.S.O., London, 1951, p. 18), is tedious to prepare in the laboratory and a more easily obtainable tervalent phosphorus compound was therefore sought as a ligand to replace one or two of the carbonyl groups of nickel carbonyl. Phosphorus trifluoride replaces up to three of the carbonyl groups of nickel carbonyl without altering the character of the complex (Chatt, *J.*, 1951, 3061) and through the courtesy of Dr. Chatt samples of his complexes roughly corresponding to $(PF_3)_2Ni(CO)_2$ were made available. Only one experiment (of five) was successful in producing a trace of *cyclo*octadiene, but this also gave a small amount of a new compound derived from both acetylene and butadiene (see below). Trimethyl and triphenyl phosphites replaced two carbonyl groups with extreme ease in cold ether solution, giving respectively the complexes $[(MeO)_3P]_2Ni(CO)_2$ as a moderately stable liquid if kept cold, and $[(PhO)_3P]_2Ni(CO)_2$ as a crystalline solid.

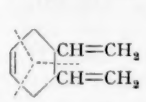
These complexes exhibited considerably greater catalytic activity than those of phosphine, and the catalyst life, as measured by the time during which the complexes catalysed the very exothermic acetylene polymerisation, was up to ten times as long. It was discovered that both phosphite complexes catalysed the formation of *cyclo*octadiene in the *absence of acetylene*, giving a product with physical constants agreeing with those quoted by Ziegler *et al.* and by Cope *et al.* (*locc. cit.*). The *cyclo*octadiene : vinyl*cyclo*hexene ratio, amounting at best to 2 : 1, was never as great in these experiments as with the acetylene-promoted phosphine catalyst. The triphenyl phosphite complex, to which most attention was directed, functioned without promotion at as low a temperature as 100°, but the conversion of the butadiene was never more than 50% in experiments lasting 48 hours, and considerable quantities of undistillable high polymer were always formed. The inclusion of calcium carbide and the antioxidant appeared to have no effect in experiments with the phosphite–carbonyl catalysts and they were therefore generally omitted. This is probably the most convenient procedure for the preparation of quantities of very pure *cyclo*octadiene.

It was established that pretreatment of the phosphite complexes with acetylene produced a markedly more active catalyst, and *cyclo*octadiene : vinyl*cyclo*hexene ratios of 5 : 1 were obtained at 100°, but the *cyclo*octadiene again had a high refractive index. Furthermore, it was occasionally possible to isolate a substantial quantity of distillable compounds boiling above the b. p. of *cyclo*octadiene, which was not obtained from experiments conducted in the absence of acetylene. The butadiene trimer was obtained (although now colourless) and shown by hydrogenation to *cyclo*dodecane to contain about 30—35% of *cyclo*dodeca-1 : 5 : 9-triene. In one experiment, a small amount of even higher-boiling material was isolated, which analysed as a butadiene tetramer, with the remarkably high refractive ind·x n_D^{20} 1·5472. Hydrogenation indicated four double bonds, and from the hydrogenated product, 5% of *cyclo*hexadecane was separated as white needles, m. p. 57°

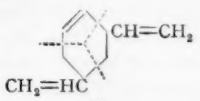
(Ruzicka and Giacomello, *Helv. Chim. Acta*, 1937, **20**, 548). A small part of the butadiene tetramer is thus present as *cyclo*hexadeca-1 : 5 : 9 : 13-tetraene.

The acetylene-promoted phosphite–carbonyl complexes also led to formation of small amounts of the compound of b. p. just above that of *cyclo*octadiene that had been observed in the successful phosphorus trifluoride experiment. By distillation of appropriately bulked fractions from a number of experiments, a compound $C_{10}H_{14}$, b. p. 169°, n_D^{20} 1·4860, was isolated, which was therefore derived from two molecules of butadiene and one molecule of acetylene. On hydrogenation 3 mols. of hydrogen were absorbed to give a saturated hydrocarbon $C_{10}H_{20}$, showing that the compound was cyclic and contained three double bonds.

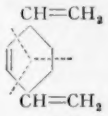
Infra-red examination showed the presence of two vinyl groups and one *cis*-1 : 2-disubstituted ethylene linkage, all unconjugated, which was confirmed by lack of reaction with maleic anhydride and dimethyl acetylenedicarboxylate. The compound was therefore almost certainly one of the isomers of divinyl*cyclo*hexene [(IV)—(VI), the dotted lines show the components]. Complete characterisation was not attempted, but the physical



(IV)



(V)



(VI)

(VII)

properties of the saturated hydrocarbon suggest that it was 1 : 2-diethyl*cyclo*hexane indicating structure (IV) for the compound $C_{10}H_{14}$. Whatever the isomer, it is noteworthy that it is formed from two molecules of butadiene both reacting in the 1 : 2-position, whereas in vinyl*cyclo*hexene and *cyclo*octadiene at least one of the butadiene molecules has reacted in the 1 : 4-position. The four-membered ring dimer of butadiene, *trans*-1 : 2-divinyl-*cyclo*butane, formed from two molecules of butadiene reacting in the 1 : 2-position (Reed, *loc. cit.*), was not detected in any of the products of this catalytic reaction.

The impurity responsible for the high refractive indices of the *cyclo*octadiene made with the acetylene-promoted catalysts was shown by ultra-violet analysis to be only partly accounted for by styrene (b. p. 144°; n_D^{20} 1·5434), which has a strong absorption band in the infra-red at 770 cm.$^{-1}$ and not at 765 cm.$^{-1}$. This was clearly demonstrated by comparison of the infra-red spectra of a pure specimen of *cyclo*octadiene containing 2% of styrene and the impure *cyclo*octadiene. Hydrogenation of a large sample of impure *cyclo*octadiene, followed by careful fractionation, led to the isolation of only ethyl*cyclo*hexane and *cyclo*octane. Hence, the impurity must have an eight-membered ring structure, and therefore *cyclo*octa-1 : 3 : 6-triene (VII) formed by reaction of one molecule of butadiene and two molecules of acetylene, or its isomerisation product, *cyclo*octa-1 : 3 : 5-triene, seem most likely to be present. Both, but especially (VII), show considerable absorption at about 765 cm.$^{-1}$ (Cope and Hochstein, *loc. cit.*; Cope, Haven, Ramp, and Trumbell, *J. Amer. Chem. Soc.*, 1952, **74**, 4868).

Early attempts to extend the cyclic polymerisation catalysed by the acetylene-promoted phosphine–carbonyl complex to substituted butadienes gave disappointing results. Isoprene, piperylene, 1 : 4- and 2 : 3-dimethylbutadiene, and 1- and 2-methoxybutadiene gave very small quantities of compounds comprised of one molecule of the diene and two or three molecules of acetylene (see Experimental). These compounds readily absorbed oxygen, and their constitutions were not established. Later, it was found that isoprene and piperylene gave substantial quantities of dimers with the acetylene-promoted phosphite–carbonyl complex but the products were not investigated in detail. Propene and *iso*butene failed to react, and vinylacetylene reacted uncontrollably giving high polymer and tar.

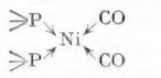
A wide variety of complexes derived from carbonyls and metal salts has been examined in the butadiene reaction, generally with acetylene added as promoter. All the results have been negative. Acetylene alone did not react with the cobalt carbonyl complexes $[Ph_3PCo(CO)_3]_2$ and $[(PhO)_3PCo(CO)_3]_2$ or the iron carbonyl complex $(Ph_3P)_2Fe(CO)_3$,

the first two being completely insoluble in all solvents, and the last so extremely stable that it was invariably recovered unchanged. The iron carbonyl–butadiene complex $C_4H_6Fe(CO)_3$ (Reihlen, *Annalen*, 1930, **482**, 161) was also extremely stable and non-catalytic in the butadiene polymerisation. Other inactive complexes included cobalt and iron nitrosocarbonyls and iron carbonyl iodide and their substituted derivatives, *e.g.*, $Ph_3PCo(NO)(CO)_2$, $(PhO)_3PCo(NO)(CO)_2$, $(Ph_3P)_2Fe(NO)_2$, and $(PhO)_3PFe(CO)_3I_2$. Butadiene did not polymerise with any metal halide derivative. The square-planar complexes of nickel halides and tri-*n*-propylphosphine (see Jensen, *Z. anorg. Chem.*, 1936, **229**, 265) generally gave highly exothermic reactions on being heated with acetylene leading to voluminous black polymers or tar, but the addition of butadiene to the reacting system gave no distillate product. A solution of the red complex $(Pr_3P)_2NiBr_2$ was converted into a deep blue liquid on treatment in solution with butadiene alone at 120°, but no butadiene polymerisation occurred.

The Reppe complexes $(Ph_3P)_2NiBr$ and $(Ph_3P)_2CuCl$ did not react. Complexes of the nickel cation which polymerise acetylene to *cyclo*octatetraene such as nickel cyanide (Reppe) and especially the nickel acetonylacetone complex (Cope and Estes, *J. Amer. Chem. Soc.*, 1950, **72**, 1128) which also readily interpolymerises acetylene and mono- and di-substituted acetylenes (Cope and Campbell, *ibid.*, 1951, **73**, 3537; 1952, **74**, 179; Cope and Smith, *ibid.*, p. 5136) failed to polymerise butadiene, and attempts to interpolymerise acetylene and butadiene led to only *cyclo*octatetraene. The carbonyls of chromium, molybdenum, and tungsten formed much high polymer but no distillable products from butadiene above 90°.

Other ligands were sought to replace some of the carbonyl groups of nickel carbonyl. Thus, *o*-phenanthroline forms chelate complexes with iron, cobalt, and nickel carbonyls (Hieber *et al.*, *Ber.*, 1932, **65**, 1082, 1090) but the isolated nickel derivative $Ni(CO)_2$–*o*-phenanthroline was found to be unstable in air. A preparation *in situ* was therefore devised in which nickel carbonyl and the base were heated with acetylene and butadiene, a procedure well adapted to the use of other bases, such as pyridine, which give very unstable pyrophoric substitution products. A series of experiments with a number of different types of organic nitrogen bases with butadiene and acetylene gave small amounts of *cyclo*octadiene, but large quantities of vinyl*cyclo*hexene, suggesting that these complexes catalyse the formation of the six-membered ring dimer of butadiene.

It is concluded that the catalytic cyclic polymerisation of butadiene to large-ring compounds is a specific property of nickel^0 compounds, possessing the partial structure (VIII).

(VIII)  (IX)

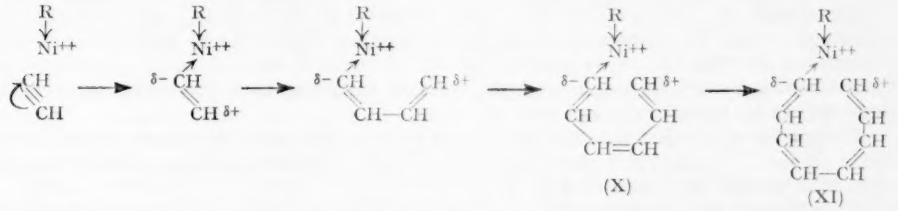
These compounds are not, of course, the active catalysts in the polymerisation but are converted into a soluble, electrophilic nickel complex by initial reaction with the unsaturated compound probably resulting in removal of one or both of the residual carbonyl groups (*e.g.*, IX). Variations in properties of the resulting complex then reside in the effects of the remaining ligands.

A theory of the mechanism by which butadiene is polymerised by the nickel carbonyl derivatives should embrace the related cyclic polymerisations of acetylene catalysed by the carbonyl derivatives which give benzene and styrene, and by the nickelous cation complexes which lead to *cyclo*octatetraene and related higher compounds. Although the formation of *cyclo*octatetraenes appears to be an exclusive property of the nickelous cation complexes, considerable quantities of aromatic products are also formed (see especially Cope and Estes, *loc. cit.*).

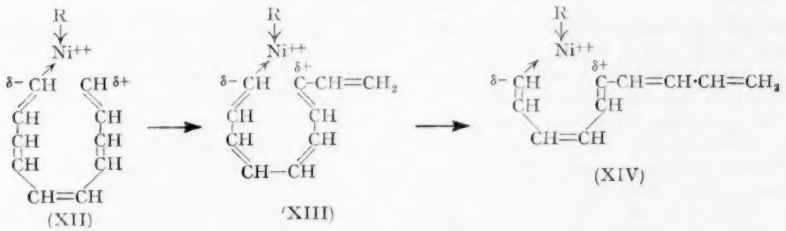
The interpolymerisation of acetylene with but-2-yne and diphenylacetylene to give 1 : 2-disubstituted *cyclo*octatetraenes led to the conclusion that the association of acetylene with the catalyst is through an electron pair of the triple bond (Cope and Campbell, *loc. cit.*; Cope and Smith, *loc. cit.*). This idea can be readily extended to butadiene, one double bond providing the electron pair for association to the catalyst and the other taking part in the polymerisation.

A partial picture of these cyclic polymerisation processes involves a steady successive build-up of the eventual ring system around the nickel atom by addition of units of either acetylene or butadiene, followed by the final break away of the nearly formed ring in a final cyclisation step. The characterisation of the 1-phenylbuta-1 : 3-diene present in the pentamer fraction from *cyclo*octatetraene preparations as the *cis*-isomer (Craig and Larrabee, *loc. cit.*; Cope and Fenton, *loc. cit.*) provides strong evidence for such a ring complex. More complete understanding is precluded by lack of evidence as to the actual nature of the active nickel complex.

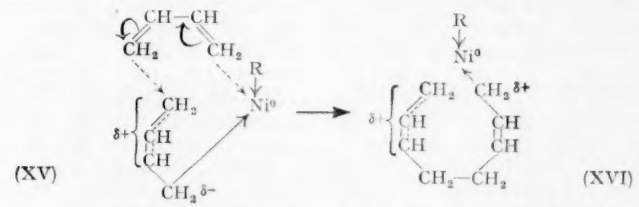
In the *cyclo*octatetraene synthesis, a succession of anionoid attacks by the acetylene on the cationoid complex, R $\longrightarrow$ Ni^{++} (where R is the co-ordinated group giving a soluble complex), leads to the sequence :



The intermediate complexes are mesomeric zwitterions which decompose by cyclisation, re-forming the initial complex and the *cyclo*polyolefin, *e.g.*, benzene from (X) and *cyclo*octatetraene from (XI). It is evident that further addition of acetylene must lead to isomerisation of the complex, presumably by successive 1 : 3-shifts in the conjugated double bond system. This is represented in the case of (XII) by changes to (XIII) and (XIV), precursors of vinyl*cyclo*octatetraene and *cis*-1-phenylbutadiene, respectively, and it is noteworthy that 1 : 2-divinylbenzene, which would require isomerisation at both ends of the carbon chain, is not formed. An analogous series of intermediates may be envisaged from complexes of nickel^0 but whereas the acetylene tetramer precursor (XI) appears to

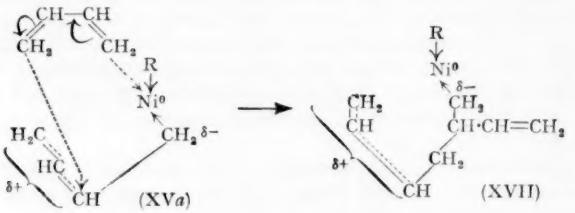


be stable with Ni^{++}, the corresponding Ni^0 complex must isomerise readily to give styrene instead of *cyclo*octatetraene. In the polymerisation of butadiene, initial anionoid attack on the cationoid nickel complex gives the zwitterion (XV), and a further molecule of



butadiene the complex (XVI), which gives *cyclo*octadiene by cyclisation and breakaway from the nickel catalyst. The formation of vinyl*cyclo*hexene involves the reaction of the

second molecule of butadiene at the allylic position of the initial intermediate (XV*a*) to give (XVII):



Repetition of this process leads to complexes from which *cyclo*dodecatriene and vinyl-*cyclo*decadiene, etc., could be formed. The formation of the large-ring compounds from butadiene, whilst underlining the remarkable cyclising properties of substituted nickel derivatives, is probably made possible by the absence of the conjugated double-bond system that is formed in complexes built up from acetylene, thus preventing substantial ring-contraction by isomerisation.

These schemes predict that the higher acetylene polymers should consist initially of a ring with one conjugated side-chain, whereas the higher butadiene polymers should contain rings with several vinyl side-chains.

No evidence of the formation of any compound with an open-chain structure has been forthcoming either in work on the polymerisation of acetylene or this work with butadiene, although such compounds would easily have been detected by their much lower refractive indices, especially in the fully hydrogenated derivatives. This suggests that the only method whereby the built-up carbon chain can become detached from the catalyst is by reaction at the other end of the chain, as indicated in the scheme. If this cyclisation does not occur, and presumably it becomes more difficult as the length of the chain increases, the complex may then initiate the long-chain polymerisation of butadiene, thus resulting in the formation of the large quantities of high polymer which always accompany the distillable polymers.

Experimental

Pressure Equipment.—Reactions involving the use of acetylene under pressure were studied in a unit comprising a stirred 1-l. autoclave, with electrical space heating, to which liquids could be introduced from a 250-c.c. storage vessel, and acetylene and nitrogen or other gases added through separate delivery pipes. All the parts were made of standard 250-atm. equipment, the acetylene lines being fitted with steel wire to decrease their volume. Copper-containing materials were excluded and all unfilled spaces packed with steel gauze. Valves in contact with acetylene were of the push-pull type and all were fitted with extended spindles for remote control from behind a brick wall. The acetylene supply was drawn from specially packed cylinders of 60 cu. ft. capacity containing no free space at the top, and a special non-return valve was incorporated immediately above the cylinder (Reppe, *Chem. Ing. Tech.*, 1950, **22**, 279). All operations were conducted within the limits of conditions laid down by Home Office Regulations (S.R. & O., 1947, No. 805).

Catalytic Polymerisation of Butadiene with Acetylene-promoted $(Ph_3P)_2Ni(CO)_2$ (with P. Harrison).—A solution of the complex $(Ph_3P)_2Ni(CO)_2$ (10·0 g.), 2 : 5-di-*tert.*-butyl-1 : 4-benzoquinone (0·2 g.), and calcium carbide (5 g.) in benzene (200 c.c.) was heated in the autoclave under an initial pressure of 7 atm. of acetylene and 3 atm. of nitrogen until promotion of the complex occurred, generally in the range 120—130° (indicated by a sudden temperature rise of about 15—20°). The mixture was then cooled to 120—130°, and butadiene (250 c.c., 176 g.) added during 2 hr. After further heating at 120—130° (generally for 2 hr.) during which time further acetylene was admitted to restore the pressure, the mixture was allowed to cool overnight. The reaction mixture was freed from unreacted butadiene (30—70 g.) by releasing the pressure through cooled receivers and slightly warming the liquid product, filtered from acetylene polymer and calcium carbide, and flash-distilled at 150°/15 mm. Final fractionation of the distillate at atmospheric pressure to remove the solvent and then under reduced pressure gave vinyl*cyclo*hexene (9—15 g.), b. p. 77°/144 mm., and *cyclo*octadiene (35—55 g.), b. p. 95—97°/144 mm., n_D^{20} 1·4945—1·4960 (Found: C, 88·9; H, 11·1. Calc. for C_8H_{12}: C, 88·9; H, 11·1%).

In a reaction time of 8·5 hr., *cyclo*octadiene (62 g., 44%) and vinyl*cyclo*hexene (17 g., 10·5%) were obtained at a butadiene conversion of 85%. Reduction of the amount of catalyst to 1 g. gave no product.

cyclo*Octa*-1 : 5-*diene*.—The hydrocarbon was characterised as 2-*chloro*cyclo*oct*-5-*enyl* 2 : 4-*dinitrophenyl sulphide*, m. p. 112—113° (cf. Kharasch and Buess, *loc. cit.*) (Found: C, 48·8; H, 4·4. $C_{14}H_{15}O_4N_2SCl$ requires C, 49·0; H, 4·4%), after crystallisation from methanol–ethanol. Ozonolysis gave pure succinic acid, m. p. and mixed m. p. 186—187° [diphenacyl ester, needles (from alcohol), m. p. and mixed m. p. 151°].

cyclo*Octene*.—The dimer (10·94 g.) was shaken in hydrogen at room temperature and pressure in ether (60 c.c.) in the presence of pre-reduced palladium–barium sulphate (3 g.; 5% Pd). Absorption ceased abruptly after 1·07 mol. had been absorbed (2600 c.c. at 20°/760 mm. Calc. for one mol. of hydrogen, 2440 c.c.). After removal of catalyst and solvent, the residue was distilled giving *cyclo*octene (9·8 g.), b. p. 144—145°, n_D^{20} 1·4700, characterised as 2-*chloro*cyclo*octyl* 2 : 4-*dinitrophenyl sulphide*, which crystallised from benzene–alcohol as needles, m. p. 140° (Found: C, 48·8; H, 4·8; Cl, 10·1. $C_{14}H_{17}O_4N_2SCl$ requires C, 48·8; H, 4·9; Cl, 10·3%), alone or mixed with a specimen made from authentic *cyclo*octene. The *cyclo*octene was further characterised by oxidation with potassium permanganate in acetone at 0—10° (Reppe, Schlichting, Klager, and Topel, *Annalen*, 1948, **560**, 1) to suberic acid, m. p. and mixed m. p. 140·5° (diphenacyl ester, m. p. and mixed m. p. 102—103°, and di-*p*-bromophenacyl ester, m. p. and mixed m. p. 143°).

cyclo*Octane*.—*cyclo*Octadiene (14·3 g.) in methanol (30 c.c.) was hydrogenated to completion at 50 lb./sq. in., Raney nickel catalyst (*ca.* 3 c.c.) being used. Removal of catalyst and solvent gave *cyclo*octane (12·1 g.), b. p. 67—68°/50 mm., m. p. 11°.

Butadiene Trimer.—The bulked residues from 15 runs (82·3 g.) were distilled (19 mm.) to give *cyclo*octadiene (18 g.), b. p. 45—47°, and liquid fractions, b. p. 60—105° (8 g.), b. p. 105—115° (16 g.), and b. p. 115—130° (16 g.) (intense blue). Refractionation of the latter fractions gave the *butadiene trimer* (13 g.), b. p. 112—114°/20 mm., n_D^{20} 1·5111 (Found: C, 89·1; H, 11·1. $C_{12}H_{18}$ requires C, 88·9; H, 11·1%).

cyclo*Dodecane*.—Hydrogenation (Adams catalyst) of the trimer (11·5 g.) in methyl acetate (35 c.c.) to completion (4795 c.c. at 20°/760 mm Calc. for 3 mol. of hydrogen: 5100 c.c.), followed by removal of catalyst and solvent, and cooling to −10°, gave crude *cyclo*dodecane (4·8 g.), which was filtered off and recrystallised from methanol–methyl acetate, forming needles (3·2 g.), m. p. 61° (Found: C, 85·7; H, 14·4. Calc. for $C_{12}H_{24}$: C, 85·6; H, 14·4%). The liquid part of the hydrogenated trimer was distilled at 144 mm. to give the following saturated hydrocarbon fractions: b. p. 100—101°, n_D^{20} 1·4708 (0·68 g.); b. p. 101—102°, n_D^{20} 1·4728 (1·08 g.); b. p. 102—103°, n_D^{20} 1·4741 (1·56 g.); b. p. 103—106°, n_D^{20} 1·4757 (1·40 g.); b. p. 106—108°, n_D^{20} 1·4787 (1·47 g.); and b. p. 108—110°, n_D^{20} 1·4829 (0·4 g., almost completely solidified on cooling to 0°).

Catalytic Polymerisation of Butadiene with Acetylene-promoted $[(MeO)_3P]_2Ni(CO)_2$.—A solution of the complex $[(MeO)_3P]_2Ni(CO)_2$ (10 g.) in benzene (250 c.c.), di-*tert.*-butylbenzoquinone (0·2 g.), and butadiene (150 c.c., 106 g.) was heated in the autoclave under an initial pressure of 6 atm. of acetylene and 3 atm. of nitrogen. After promotion of the catalyst, the temperature was maintained at 120° for 3 days, butadiene (150 c.c.) being added at the beginning of the second and the third day. Acetylene was added occasionally during the experiment, resulting in slight rises in temperature (thus showing continued activity of the catalyst). After cooling, the reaction product was steam-distilled to separate distillable products from high polymer. Final fractionation at 144 mm. gave vinyl*cyclo*hexene (38 g.), b. p. 74—78°, *cyclo*octadiene (49 g.), b. p. 95—96°, n_D^{20} 1·4971, and a fraction (4 g.), b. p. 98—120°. In other similar experiments, up to 30 g. of trimer have been obtained from a single run by prolonging the steam-distillation of the crude products. Hydrogenation as before gave 30—35% yields of *cyclo*dodecane.

cyclo*Hexadecane*.—By very prolonged (8 hr.) steam-distillation of the products of a reaction catalysed by acetylene-promoted $[(MeO)_3P]_2Ni(CO)_2$, a heavy oil (8·2 g.) was isolated. Distillation gave butadiene trimer, b. p. 56—80°/0·8 mm. (4·4 g.), and tetramer, b. p. 93—98°/0·8 mm., n_D^{20} 1·5472 (2·4 g.), 98—108°/0·8 mm., n_D^{20} 1·5468 (1·0 g.). On hydrogenation in ethyl acetate (20 ml.) with Adams catalyst, the tetramer fraction, b. p. 93—98°/0·8 mm. (2·2 g.), absorbed 1037 c.c. (Calc. for 4 mol. of hydrogen, 977 c.c.). Removal of catalyst and solvent, followed by cooling to −50°, led to the separation of crude *cyclo*hexadecane, which was filtered off and recrystallised from methyl acetate–methanol, forming white needles (0·1 g.), m. p. 57° (Found: C, 85·6; H, 14·3. Calc. for $C_{16}H_{32}$: C, 85·6; H, 14·4%).

Catalytic Polymerisation of Butadiene with Acetylene-promoted $[(PhO)_3P]_2Ni(CO)_2$.—A solution of $[(PhO)_3P]_2Ni(CO)_2$ (10 g.), di-*tert.*-butylbenzoquinone (0·2 g.), and butadiene (250 c.c., 176 g.) in benzene (200 ml.) was heated under an initial pressure of 7 atm. of acetylene and 3 atm. of nitrogen for 2·5 days at 110°, acetylene being added intermittently. The products were worked up by steam-distillation and finally fractionated at 144 mm. to give vinyl*cyclo*hexene (26 g.), *cyclo*octadiene (7·9 g.), b. p. 90—93°; b. p. 93—96°, n_D^{20} 1·4931 (36·7 g.); b. p. 96—97°, n_D^{20} 1·4951 (60·1 g.); b. p. 97—100°, n_D^{20} 1·4945 (12·3 g.); and material, b. p. 100—110°, n_D^{20} 1·4909 (4·1 g.); and b. p. 110—124°, n_D^{20} 1·4852 (6·6 g.). In other runs, butadiene trimer (10—30 g.) was also obtained.

Catalytic Polymerisation of Butadiene with Non-promoted $[(PhO)_3P]_2Ni(CO)_2$.—A solution of $[(PhO)_3P]_2Ni(CO)_2$ (10 g.) and di-*tert.*-butylbenzoquinone (0·2 g.) in benzene (200 ml.) was heated under an initial pressure of 3 atm. of nitrogen for 4 days at 100°. Steam-distillation and fractionation at 144 mm. gave vinyl*cyclo*hexene (32 g.) and pure *cyclo*octadiene (63·7 g.), b. p. 97°, n_D^{20} 1·4935, n_D^{25} 1·4912, m. p. −69·5.

*Divinyl*cyclo*hexene*.—Fractions having b. p. 98—120°/144 mm. from a number of experiments with acetylene-promoted phosphite–nickel carbonyl catalysts were bulked and fractionated to give *divinyl*cyclo*hexene*, b. p. 108—109°/144 mm. (169°/760 mm.), n_D^{20} 1·4860 (Found: C, 89·4; H, 10·5. $C_{10}H_{14}$ requires C, 89·6; H, 10·4%).

*Diethyl*cyclo*hexane*.—Divinyl*cyclo*hexene (2·5 g.) was hydrogenated to completion in methyl acetate (15 c.c.) in the presence of Adams catalyst (1510 c.c. were absorbed. Calc. for 3 mol. of hydrogen, 1560 c.c.). The catalyst and solvent were removed and the residue distilled to give diethyl*cyclo*hexane, b. p. 173—175°, n_D^{20} 1·4495 (Found: C, 85·5; H, 14·4. Calc. for $C_{10}H_{20}$: C, 85·6; H, 14·4%). Buck *et al.* (*J. Inst. Pet.*, 1948, **37**, 399) gives b. p. 177°, n_D^{20} 1·4471, for (presumably *cis*-) 1 : 2-diethyl*cyclo*hexane.

Reaction of Acetylene with Substituted Butadienes catalysed by $(Ph_3P)_2Ni(CO)_2$.—A solution of the complex $(Ph_3P)_2Ni(CO)_2$ (5 g.) in benzene (100 ml.) with di-*tert.*-butylbenzoquinone (0·2 g.) and calcium carbide (5 g.) was heated under an initial pressure of 6—7 atm. of acetylene and 3 atm. of nitrogen until promotion of the catalyst occurred. The substituted butadiene was then added (1 hr.) to the mixture at 120—130°, and heating continued for 3—4 hr. The reaction product was then filtered, flash-distilled, and fractionated, giving results collected in the Table.

Trialkyl and Triaryl Phosphite Complexes of Nickel Carbonyl.—Stoicheiometric quantities of nickel carbonyl and the phosphite ligand were mixed in ether solution (compare Rose and

Products from the reaction of acetylene with substituted butadienes.

Diene	Products, wt., g.	b. p./mm.	n_D^{20}	Analysis, Found, % C	H	Formula	Required, % C	H
1-Methoxybutadiene	4·0	67°/10	1·5149	80·1	8·6	$C_5H_8O + 2C_2H_2$	79·4	8·8
(25·5 g.)	1·0	78°/10	1·5225	79·9	8·5	$C_5H_8O + 3C_2H_2$	81·5	8·6
2-Methoxybutadiene	1·4	65—67°/10	1·5282	82·0	8·6	—	—	—
(30·0 g.)	3·0	70°/10	1·5375	82·3	8·5	—	—	—
2 : 3-Dimethylbutadiene	4·0	47—48°/10	1·4930	89·8	10·2	$C_6H_{10} + C_2H_2$	88·9	10·1
(109 g. in 2 expts.;	1·9	50—52°/10	1·5044	90·1	10·2	$C_6H_{10} + 2C_2H_2$	89·6	10·4
products bulked)						$C_6H_{10} + 3C_2H_2$	90·0	10·0
1 : 4-Dimethylbutadiene	1·0	48—49°/10	—	89·8	10·1	$(C_6H_{10})_2$	87·8	12·2
(31 g.)	2·0	50—59°/10	—	90·2	9·9	—	—	—
Isoprene (42·5 g.)	3·5	44—46°/10	1·5080	89·9	10·1	$C_5H_8 + C_2H_2$	88·2	11·8
						$C_5H_8 + 2C_2H_2$	90·0	10·0
						$C_5H_8 + 3C_2H_2$	90·4	9·6
Piperylene (44·3 g.)	3·9	44—45°/10	1·5010	89·8	10·2	$(C_5H_8)_2$	88·2	11·8

Statham, *loc. cit.*). The theoretical quantity of carbon monoxide was evolved briskly and after slight warming to complete the reaction, the ether was removed on a warm-water bath, finally under slight vacuum. The resulting *complexes*, obtained in nearly quantitative yields, were stored under nitrogen at −10°. The triphenyl phosphite complex was obtained as colourless needles, m. p. 95°, from light petroleum (b. p. 40—60°)–ether (Found: C, 62·2; H, 4·2; P, 8·4; Ni, 7·7. $C_{38}H_{30}O_8P_2Ni$ requires C, 62·1; H, 4·1; P, 8·4; Ni, 8·0%).

Triphenyl Phosphite Complex of Cobalt Carbonyl (G. H. Whitfield).—A filtered ethereal solution of cobalt carbonyl (30 g.) was treated with an ethereal solution of triphenyl phosphite (138 g.) at room temperature. Carbon monoxide was rapidly evolved (4300 c.c. Calc. for 2 mol. 4200 c.c. at 18°), and the mixture was finally warmed under reflux to complete the

reaction. The complex $[(PhO)_3PCo(CO)_3]_2$ (66·5 g.) was obtained as silky brown needles, m. p. 173° (decomp.), totally insoluble in common organic solvents.

Complexes of Cobalt Nitrosocarbonyl.—(a) *With triphenylphosphine.* A solution of cobalt nitrosocarbonyl (5 g.) in ether (25 c.c.) was treated with triphenylphosphine (7·6 g.) in ether (15 c.c.) and warmed; carbon monoxide was evolved, and final distillation of the ether gave the *complex* $Ph_3PCo(NO)(CO)_2$, maroon prisms, m. p. 125° (decomp.), from light petroleum (b. p. 60—80°) (Found: C, 59·8; H, 3·6; N, 3·5; P, 7·3. $C_{20}H_{15}O_3NPCo$ requires C, 59·0; H, 3·7; N, 3·4; P, 7·6%).

(b) *With triphenyl phosphite* (G. H. Whitfield). No reaction occurred between cobalt nitrosocarbonyl and triphenyl phosphite in boiling ether. A solution of cobalt nitrosocarbonyl (11·5 g.) and triphenyl phosphite (20·6 g.) in ether (100 c.c.) was heated under an initial pressure of 50 atm. of carbon monoxide for 5 hr. at 120°. Removal of the solvent from the residue followed by recrystallisation from methanol gave the *complex* $(PhO)_3PCo(NO)(CO)_2$ (19·6 g.) as orange rhombic prisms, m. p. 55° (Found: N, 3·1. $C_{20}H_{15}O_6NPCo$ requires N, 3·1%). Alternatively, excess of pure dry nitric oxide was passed slowly over the complex $[(PhO)_3P)_2Co(CO)_3]_2$ (27 g.) at 100° in an apparatus previously swept with nitrogen. After 2 hr., the nitrosocarbonyl complex was extracted with ether, filtered, and finally crystallised from methanol (16·1 g.).

Triphenyl Phosphite Complex of Iron Tetracarbonyl Iodide (G. H. Whitfield).—A solution of iron tetracarbonyl iodide (20 g.) in ether (200 c.c.) was treated at 20° with a solution of triphenyl phosphite (15 g.) in ether (50 c.c.). After 2 hr., 1150 c.c. of carbon monoxide had been evolved (Calc. for 1 mol., 1130 c.c. at 18°/760 mm.) and large purple prisms of the *complex* $(PhO)_3PFe(CO)_3I_2$ were deposited (28 g.), m. p. 115° (decomp.) (Found: P, 4·1. $C_{21}H_{15}O_6PI_2Fe$ requires P, 4·4%).

Triphenyl Phosphine Complex of Iron Nitrosocarbonyl.—Iron nitrosocarbonyl (2 g.) (Hieber, F.I.A.T. Review of German Science, 1939—1946, Inorganic Chemistry, Part II, p. 129) in ether (10 c.c.) was treated with triphenylphosphine (6 g.) in ether (20 ml.), and warmed. The *complex* $(Ph_3P)_2Fe(NO)_2$ (4·2 g.) was recrystallised from benzene, forming black plates, m. p. 195—198° (decomp.) (Found: C, 67·4; H, 4·5. $C_{36}H_{30}O_2N_2P_2Fe$ requires C, 67·6; H, 4·7%).

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Studies of Trifluoroacetic Acid. Part XI. The Reactions of Diazonium Trifluoroacetates with Aromatic Compounds to give Diaryls.*

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N-Acetylarylamines react with alkyl nitrites in trifluoroacetic anhydride, and from the resultant mixtures the *N*-nitroso-derivatives are precipitated when water is added, whilst diphenyls are formed by treatment with benzene. Solutions of *N*-trifluoroacetylarylamines in the nitrosating agents, aqueous diazonium trifluoroacetates, solid diazonium acid trifluoroacetates (cf. *J.*, 1953, 3081), and aqueous solutions of diazonium chlorides containing added trifluoroacetate ions, all also give diphenyl derivatives when treated with aromatic compounds. Diazonium salts of other perhalogeno-carboxylic acids behave similarly.

There have been recently many investigations of the production of diaryl compounds by homolytic aromatic substitution (see, *inter al.*, Hey, *J.*, 1952, 1974; Waters, *Ann. Reports*, 1952, **49**, 118; Hey, Nechvatal, and Robinson, *J.*, 1951, 2892; Huisgen and Horeld, *Annalen*, 1949, **562**, 137; Bachmann and Hoffman, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, 1944, p. 224). Among the important arylating agents are acylarylnitrosamines (Fischer, *Ber.*, 1876, **9**, 463; Bamberger, *Ber.*, 1897, **30** 366) which have been made from acylarylamines by nitrosation with nitrous fumes (Haworth and Hey, *J.*, 1940, 361) or with nitrosyl chloride (France, Heilbron, and Hey, *ibid.*, p. 369).

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The present work began with the application, to the nitrosation of acylarylamines, of mixtures of trifluoroacetic anhydride and alkyl nitrites. Such mixtures give diazonium salts with reactive aromatic compounds; this reaction presumably proceeds by nitrosation to give nitroso-compounds, which then react further with nitric oxide present in the mixture (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1952, 1695). It was found that solutions of a number of *para*-substituted acetanilides in ethyl or amyl nitrite–trifluoroacetic anhydride reacted with benzene under conditions similar to those usually employed with nitroso-acetanilides, to give the corresponding diphenyl derivatives (see Table 1). If a solution of the anilide in the nitrosating mixture was poured into water the *N*-nitrosoacetanilide derivative was precipitated, and in the one case tried, addition of alkaline β-naphthol gave the corresponding coupling product. Sodium nitrite can be used instead of an alkyl nitrite in the process.

Attempts were made next to extend the earlier work on acylarylamines by nitrosating *N*-trifluoroacetylarylamines (Bourne, Henry, Tatlow, and Tatlow, *J.*, 1952, 4014). Nitrosation of trifluoroacetanilide in trifluoroacetic acid solution with nitrous fumes was slow. No *N*-nitroso-derivative was precipitated when water was added to the solution, though unchanged anilide was obtained. However, after a relatively long time, addition of β-naphthol in alkali to the aqueous phase precipitated some azo-β-naphthol derivative (Table 2). Trifluoroacetanilide and its analogues reacted with trifluoroacetic anhydride–ethyl nitrite, but no precipitate was formed when water was added, though addition of β-naphthol in alkali gave the analogous azo-β-naphthol coupling derivative in good yield. Also, a solution of a trifluoroacetanilide in the nitrosating medium gave with benzene the expected unsymmetrical diphenyl (see Table 1). In general, the reactions were carried out for about 24 hours at 10—15° and then the benzene was evaporated at up to 100°. In one case a significant yield of diphenyl was obtained when the mixture was merely refluxed for 1 hour. Nitrosations, with trifluoroacetic anhydride–nitrite, of *N*-acetyl and -trifluoroacetyl derivatives of amines containing certain groups such as nitro or trifluoromethyl were more difficult than with other types of anilides, and in one case, that of 4-nitro-3-trifluoromethyltrifluoroacetanilide, no reaction was detected.

Thus, it was shown that trifluoroacetic anhydride–nitrite mixtures are effective for the *N*-nitrosation of acylarylamines, though, as frequently occurs, the yields obtained in the diaryl synthesis were not high—they did not often exceed 40%. Mechanisms which may be advanced to explain the reactions of trifluoroacetic anhydride–oxy-acid mixtures (Bourne, Randles, Stacey, Tatlow, and Tedder, unpublished work) and involve the formation, first, of the appropriate unsymmetric anhydride derived from trifluoroacetic acid and the oxy-acid, appear to be in accord with these nitrosations.

The experiments described above suggested that, though nitrosation of trifluoroacetylated arylamines occurred, the products might well be trifluoroacetates and not *N*-nitroso-derivatives. Accordingly, aromatic amines were diazotized in trifluoroacetic acid, and the diazonium solutions were treated with benzene in attempts to promote the diaryl synthesis. Aniline was diazotised in benzene with ethyl nitrite–trifluoroacetic acid in the absence of water and, after 24 hours at room temperature, a significant yield of diphenyl was isolated. Further, several *para*-substituted aromatic amines were diazotized with sodium nitrite in aqueous trifluoroacetic acid, and the aqueous solutions were stirred with benzene: again the corresponding unsymmetrical diphenyls were obtained (see Table 3), though the yields generally were not high (10—25%). As was expected with a heterogeneous reaction of this type, stirring was necessary, a very poor yield otherwise resulting. When aqueous benzenediazonium chloride or aqueous *p*-chlorobenzenediazonium chloride was stirred with benzene under similar conditions no diaryl was found in the products, nor was it if acetic acid was added to the former mixture. However, when trifluoroacetic acid or sodium trifluoroacetate was added to the aqueous diazonium chloride–benzene systems, the corresponding diphenyl was formed in moderate yield (10—20%) (see Table 4). As would be expected, these yields fell as the aqueous phase was made more dilute.

Earlier work (Pettit, Stacey, and Tatlow, *J.*, 1953, 3081) has shown that diazotizations of certain aromatic amines in trifluoroacetic or other perhalogenocarboxylic acids give solid diazonium acid salts, $Ar{\cdot}N_2^+\}R{\cdot}CO_2^-, R{\cdot}CO_2H$, which are sparingly soluble in water.

Such solid salts have now been found to react with benzene, and, after either many hours at *ca.* 15° or a short time at higher temperatures, diphenyls were isolated (Table 5). Salts derived from trifluoroacetic, heptafluorobutyric, and trichloroacetic acid were all used successfully in reactions of this type. Also, in analogous reactions, aqueous diazonium salts derived from the two last acids gave diphenyls if treated with benzene.

In all the reactions described so far, the diazonium, or related, components were treated with benzene to avoid the formation of isomeric diphenyls and so to enable a ready assessment to be made of the scope of the process. In other cases, however, benzene derivatives were treated with diazonium salts. Toluene-*p*-diazonium acid trifluoroacetate was treated at 100° with methyl benzoate and with toluene, and its aqueous solution was treated with the same liquids at 25°. In all cases it appeared that mixtures of isomers were formed and, from these, very small yields of the *p*-substituted products, 4-carbomethoxy-4′-methyl- and 4 : 4′-dimethyl-diphenyl, respectively, were obtained. Though only the *para*-isomers could be isolated, these particular products would almost certainly crystallise most readily from such mixtures so that little information on directing effects is provided by these experiments.

It must be emphasised that the work described in this paper was of an introductory nature only, and that no systematic attempts have been made to find the best reaction conditions, to obtain optimum yields, to identify by-products, or to study the reactions in a detailed quantitative fashion. The preliminary results indicate, however, that the nitrosating activity of trifluoroacetic anhydride–nitrite mixtures may find useful applications, and also that diazonium trifluoroacetates, and diazonium salts of other perhalogenocarboxylic acids, possess interesting properties. In general, diaryls are formed from the reactions of aromatic derivatives with diazo-compounds derived from strong acids, (*a*) in aqueous alkali (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339; Gomberg and Pernert, *ibid.*, 1926, **48**, 1372), (*b*) in aqueous sodium acetate (Elks, Haworth, and Hey, *J.*, 1940, 1284), or (*c*) when they are stabilised with sulphonic acids or metallic chlorides and in the presence of acetic acid–sodium acetate or sodium carbonate (Hodgson and Marsden, *J.*, 1940, 208). Dry solid aromatic diazonium chlorides can decompose in a homolytic manner (Waters, *J.*, 1939, 864, and papers quoted therein) and with anhydrous aluminium chloride and aromatic compounds give diaryls (Möhlau and Berger, *Ber.*, 1893, **26**, 1196, 1994), but there seem to be few reports of the production of unsymmetric diaryls from aromatic compounds and acidic aqueous solutions of diazonium salts of strong acids other than the early experiments of Hirsch (*Ber.*, 1890, **23**, 3705; 1892, **25**, 1973). Though aqueous diazonium salts and pyridine give phenylpyridines an excess of the base is apparently necessary (Haworth, Heilbron, and Hey, *J.*, 1940, 349). Diazonium salts of perhalogenocarboxylic acids thus seem to occupy a unique position. Their aqueous solutions exhibit typical reactions of diazonium salts of strong acids [*i.e.*, they undergo simple replacement and coupling reactions (Pettit, Stacey, and Tatlow, *loc. cit.*)] and yet these solutions, as well as the solid acid salts, and non-aqueous systems containing diazonium perhalogenocarboxylates, can all react with aromatic nuclei to give diaryls, even under acidic conditions. In this they resemble the diazoacetates, even though the conditions of reaction of the two species in the diaryl synthesis may differ considerably.

Current ideas on the decomposition of nitrosoacetanilides and diazoacetates (Huisgen and his co-workers, *Annalen*, 1949, **562**, 137; 1951, **573**, 163, 181; **574**, 157, 171, 184; DeTar, *J. Amer. Chem. Soc.*, 1951, **73**, 1446; Hey, Stuart-Webb, and Williams, *J.*, 1952, 4657, and papers mentioned therein) may well explain the reactions of diazonium perhalogenocarboxylates also. Although the latter are probably ionised to a considerable extent in aqueous acid, the alternative hypothesis of Hodgson (*J.*, 1948, 348) does not appear to give a satisfactory explanation of their reactions, in particular of the effect of addition of trifluoroacetate ions to diazonium chlorides. We suggest tentatively that it is more likely that, in these compounds, there can exist an equilibrium between ionic and some type of covalent structure and that the latter can react with aromatic compounds in substitutions of the homolytic type. If such an equilibrium does exist there is, probably, only a small concentration of covalent-type material, since diazonium acid trifluoroacetates appear to be largely dissociated in dilute aqueous solutions (Pettit, Stacey, and Tatlow, *loc. cit.*).

Experimental

Nitrosations of Acetylamines with Amyl Nitrite–Trifluoroacetic Anhydride and Conversions into Diphenyls.—Trifluoroacetic anhydride was added slowly to amyl nitrite at −10°. After 5 min., the anilide was added slowly and with shaking, and after a further 20 min. solution was stirred with benzene (25 c.c.) for 24 hr. at 15°. The dark liquid was then evaporated *in vacuo*, finally at 100°, and the tarry residue was distilled in steam. The distillate was extracted with ether, the extracts were dried ($MgSO_4$), filtered, and evaporated, and the residue was recrystallised from aqueous ethyl alcohol to give the diphenyl. The results of these experiments are given in Table 1.

Diphenyl from Acetanilide Nitrosated by Sodium Nitrite–Trifluoroacetic Anhydride.—Trifluoroacetic anhydride (4·95 g.) was added slowly to sodium nitrite (1·52 g.) at −10°, and then acetanilide (2·72 g.) was introduced. After 30 min. the mixture was stirred with benzene (30 c.c.) for 24 hr. at 15°. Diphenyl (0·90 g.), m. p. and mixed m. p. 69°, was isolated as before.

Nitrosations of Acetylamines with Ethyl Nitrite–Trifluoroacetic Anhydride and Conversions into Diphenyls.—(*a*) Trifluoroacetic anhydride (2·70 g.) was mixed with ethyl nitrite (0·85 g.) at −10°, and after 5 min. acetanilide (1·33 g.) was added slowly. After 20 min. at −10° the mixture was poured into an excess of alkaline β-naphthol, to give phenylazo-β-naphthol (from ethyl alcohol) (1·33 g.), m. p. and mixed m. p. 130—132°.

(*b*) Acetanilide was nitrosated as in (*a*), and the mixture was poured into ice-water. The precipitate was filtered off, washed with water, and dried; it was *N*-nitrosoacetanilide (0·86 g.), m. p. 44—48° (decomp.), which decomposed vigorously when heated. Grieve and Hey (*J.*, 1934, 1797) gave m. p. 51—52° (decomp.). Addition of alkaline β-naphthol to the filtrate and washings afforded phenylazo-β-naphthol (0·30 g.), m. p. and mixed m. p. 131°. *N*-Nitrosoanilides were obtained similarly from *p*-methylacetanilide and from *p*-chloroacetanilide.

(*c*) Various *N*-acetylamines were nitrosated as in (*a*) and each mixture was stirred for 24 hr. at 15° with benzene (25 c.c.) and then worked up as before. The experiments are summarised in Table 1.

Table 1. *Diphenyls from N-acylamines nitrosated by alkyl nitrite–trifluoroacetic anhydride mixtures.*

Reactants						Diphenyl products 4-X·C_6H_4·Ph		
N-Acylamine *p*-X·C_6H_4·NH·COR			Alkyl nitrite A·O·NO		$(CF_3·CO)_2O$		Yield	M. p. and
X	R	g.	A	g.	(g.)	X	(g.)	mixed m. p.
H	Me	1·35	Amyl	1·32	2·55	H	0·50	69°
Cl	,,	1·77	,,	,,	,,	Cl	0·34	75—76
Me	,,	1·48	,,	,,	,,	Me	0·35	45—47
NO_2 [a]	,,	1·78	,,	,,	,,	NO_2	0·27	113—114
H	,,	1·36	Et	0·85	,,	H	0·70	69
Me	,,	1·49	,,	0·81	3·00	Me	0·27	45—46
Cl	,,	1·71	,,	,,	2·55	Cl	0·63	75—76
CF_3	,,	1·48	,,	0·85	2·70	CF_3	0·37	70 [b]
NO_2 [a]	,,	1·84	,,	0·81	2·55	NO_2	0·12	113—114
H	CF_3	1·71	,,	0·85	,,	H	0·68 [c]	68—70
,, [d]	,,	1·91	,,	,,	,,	,,	0·59	,,
Me	,,	1·01	,,	0·54	1·50	Me	0·31	46—47
MeO	,,	1·63	,,	0·76	2·40	MeO	0·16	87—89
NO_2 [a,e]	,,	1·94	,,	1·30	3·90	NO_2	0·11	113—114

[a] Complete solution of the anilide in the nitrosating mixture was not achieved. [b] Pettit and Tatlow, *J.*, 1954, 1071, gave m. p. 70°. [c] Found: C, 93·8; H, 6·5. Calc. for $C_{12}H_{10}$: C, 93·5; H, 6·5%. [d] In this experiment, after the addition of the benzene, the temperature of the mixture was raised progressively to 100° during 1 hr., gas evolution having then ceased. [e] Unchanged anilide (0·88 g.), m. p. and mixed m. p. 146—150°, and *p*-nitroaniline (0·15 g.), m. p. and mixed m. p. 143—145°, were isolated also.

Trifluoroacetyl Derivatives of Amines.—These were prepared as described previously (Bourne, Henry, Tatlow and Tatlow, *loc. cit.*). **4-*Nitro*-3-*trifluoromethyltrifluoroacetanilide***, m. p. 115—116·5° (yield 90% after recrystallisation from benzene–light petroleum), was made similarly (Found: C, 36·0; H, 1·2; F, 37·7. $C_9H_4O_3N_2F_6$ requires C, 35·8; H, 1·3; F, 37·7%).

Nitrosations of Trifluoroacetylamines and Conversions into Diphenyls.—(*a*) To a mixture of ethyl nitrite (0·18 g.) and trifluoroacetic anhydride (0·52 g.) at −10° was added trifluoroacet-

anilide (0·30 g.). After being shaken for 20 min. the mixture, which was then homogeneous, was poured into alkaline β-naphthol. Recrystallised from ethyl alcohol the precipitate, phenylazo-β-naphthol (0·31 g.), had m. p. and mixed m. p. 130—132°.

(*b*) Trifluoroacetanilide was added in small portions to a mixture of ethyl nitrite and trifluoroacetic anhydride which was cooled to −5°. About 15 min. after the completion of the addition a spontaneous reaction occurred and the residual solid dissolved. Benzene (25 c.c.) was added and the mixture was stirred at 15° for 24 hr. (a small lower layer persisted throughout) and was then worked up as before. Experiments of this type are summarised in Table 1.

(*c*) A cooled solution of trifluoroacetanilide (1·81 g.) in benzene (25 c.c.) was added slowly and with shaking to a solution of ethyl nitrite (0·90 g.) in trifluoroacetic anhydride (3·0 g.) and the mixture was stirred for 24 hr. Diphenyl (0·48 g.), m. p. and mixed m. p. 69—70°, was obtained.

(*d*) When 4-nitro-3-trifluoromethyltrifluoroacetanilide was treated as described in expt. (*b*) no diphenyl derivative was detected; the anilide (81%) was recovered.

Nitrosations of Trifluoroacetanilide with Nitrous Fumes.—(*a*) A stream of nitrous fumes (made from concentrated aqueous sodium nitrite and dilute sulphuric acid) was passed into a solution of trifluoroacetanilide in trifluoroacetic acid at 5—10°. A dark colour had developed after *ca.* 30 min. The solution was poured into water, the colour disappearing, and a colourless precipitate of trifluoroacetanilide was formed. The aqueous filtrate was treated with alkaline β-naphthol. The results are given in Table 2.

(*b*) Nitrous fumes were passed into a solution of trifluoroacetanilide (0·53 g.) in glacial acetic acid (10·0 c.c.) at 5—10° for 4½ hr. The green liquid was then poured into water, and the

TABLE 2. *Nitrosations of trifluoroacetanilide with nitrous fumes.*

$Ph\cdot NH\cdot CO\cdot CF_3$ (g.)	$CF_3\cdot CO_2H$ (c.c.)	Time of nitrosation (hr.)	Recovered $Ph\cdot NH\cdot CO\cdot CF_3$ (g.)	Phenylazo-β-naphthol (g.)	Total recovery (%)
1·20	14·0	0·5	0·94	—	78
1·01	5·0	2·5	0·56	0·07	60
0·47	3·0	5·0	0·12	0·17	53

TABLE 3. *Diphenyls from aqueous diazonium trifluoroacetates and benzene.*

Reactants							Diphenyl produced $4\text{-}X\cdot C_6H_4\cdot Ph$		
Amine $4\text{-}X\cdot C_6H_4\cdot NH_2$		$CF_3\cdot CO_2H$	H_2O	$NaNO_2$	H_2O	Benzene		Yield	M. p. and
X	g.	(g.)	(c.c.)	(g.)	(c.c.)	(c.c.)	X	(g.)	mixed m. p.
H	4·60	15·0	0	4·00	10·0	40	H	1·80	69°
Me [a]	1·07	3·4	7·0	0·89	2·0	25	Me	0·14	43—46
OMe	1·29	3·4	2·0	0·92	2·0	25	OMe	0·48	86—89
Cl [a]	1·22	3·7	5·0	0·82	2·0	20	Cl	0·21	74—76
NO_2 [b]	1·37	4·0	1·0	0·75	1·5	25	NO_2	0·21	112—113
CF_3 [b]	1·80	3·7	1·0	0·85	1·5	25	CF_3	0·41 [d]	68—70
H [c]	0·98	3·0	1·5	0·85	2·0	25	H	0·08	67—68

[a] Some solid diazonium acid salt was present initially. [b] The nitrite was added rapidly to the amine to avoid the formation of diazoamino-compounds. [c] No stirring was applied in the reaction between the diazonium salt and the benzene. [d] Found: C, 70·1; H, 4·0. Calc. for $C_{13}H_9F_3$: C, 70·3; H, 4·1%.

precipitate was filtered off and recrystallised to give trifluoroacetanilide (0·24 g.), m. p. and mixed m. p. 88—89°. The aqueous filtrate gave no red precipitate when treated with alkaline β-naphthol.

When a solution of acetanilide in trifluoroacetic acid was treated similarly, *N*-nitrosoacetanilide (11%), m. p. 48—50° (decomp.), and phenylazo-β-naphthol (15%), m. p. and mixed m. p. 132°, were obtained.

Diphenyl Derivatives from Aqueous Diazonium Trifluoroacetate Solutions.—The amine, in trifluoroacetic acid, was treated at *ca.* 5° with aqueous sodium nitrite. Benzene was then added and the mixture was stirred at 23° for 24 hr. The organic layer was separated, washed with aqueous sodium hydroxide, then with water, and dried ($MgSO_4$). After filtration and evaporation the residue was distilled in steam, and the product was isolated from the distillate and crystallised in the normal way. The results of the experiments of this type are given in Table 3.

Diphenyl from the Reaction of Benzene with Aniline Diazotised in Trifluoroacetic Acid–Ethyl Nitrite.—Ethyl nitrite (4·5 g.), in benzene (15 c.c.), was added slowly to aniline (4·40 g.) and

trifluoroacetic acid (15·0 g.), in benzene (25 c.c.), at 5—8°. The mixture was stirred at 10—15° for 24 hr. The volatile constituents were then evaporated, and the residue was steam-distilled, etc., to give diphenyl (2·22 g.), m. p. and mixed m. p. 69—70°.

Diphenyl from Benzene and Aqueous Benzenediazonium Chloride–Trifluoroacetate.—The amine was diazotised in the normal manner with concentrated hydrochloric acid and aqueous sodium nitrite. The series of experiments summarised in Table 4 was carried out by treating such diazonium solutions, in the presence of the addenda described, with benzene at 23° for 24 hr. The diphenyl formed was isolated as usual. No diphenyl was detected in the product when no trifluoroacetate was present.

Reactions of Solid Diazonium Perhalogeno-carboxylates with Benzene.—Diazonium acid salts prepared as described previously (Pettit, Stacey, and Tatlow, *loc. cit.*) were treated with benzene under the conditions given in Table 5, the product being isolated in the normal manner.

Diphenyl from Aqueous Benzenediazonium Perhalogeno-carboxylates and Benzene.—(*a*) Aniline (0·98 g.) in heptafluorobutyric acid (6·6 g.) and water (2·1 c.c.) was diazotized with aqueous sodium nitrite. The solution was stirred at 25° for 24 hr. with benzene (50 c.c.), and, after isolation as usual, diphenyl (0·26 g.), m. p. and mixed m. p. 67—69°, was obtained.

TABLE 4. *Diphenyls from diazonium chlorides, trifluoroacetates, and benzene.*

Amine 4-X·C_6H_4·NH_2		Conc. HCl	$NaNO_2$	H_2O	Benzene	Addenda		Diphenyl 4-X·C_6H_4·Ph	
X	g.	(c.c.)	(g.)	(c.c.)	(c.c.)	Formula	g.	g.	M. p. and mixed m. p.
H	4·50	11·0	4·00	15·0	40	—	—	—	—
H	0·96	3·0	0·78	4·0	20	CH_3·CO_2H	1·8	—	—
H	0·91	3·0	0·81	13·0	20	CF_3·CO_2Na	3·75	0·11 [a]	68—70°
H	1·91	5·6	1·60	6·0	30	,,	7·24	0·60 [a]	,,
H	1·95	6·0	1·59	8·0	20	CF_3·CO_2H	6·60	0·45 [a]	,,
H	4·00	13·0	3·20	11·0	50	,,	0·69	0·20 [a]	67—69
Cl	8·00	20·0	5·00	20·0	100	—	—	—	—
Cl	1·40	5·0	1·00	5·0	50	CF_3·CO_2H	3·00	0·20 [b]	74—76

[a] X = H. [b] X = Cl.

TABLE 5. *Diphenyls from benzene and diazonium acid salts.*

Diazonium acid salt			Benzene	Reaction conditions		Diphenyl produced		
Amine	Acid	g.	(c.c.)	Time (hr.)	Temp.	Formula	g.	M. p. and mixed m. p.
p-C_6H_4Me·NH_2	CF_3·CO_2H	1·44	15	24	15°	4-Me·C_6H_4·Ph	0·30	45—47°
p-C_6H_4Cl·NH_2	CF_3·CO_2H	4·36	50	2	80	4-Cl·C_6H_4·Ph	0·41 [a]	75—76
,,	C_2F_7·CO_2H	6·50	50	2	80	,,	0·66	,,
,,	CCl_3·CO_2H	23·2 [b]	250	2	80	,,	1·90	,,

[a] Found: C, 76·2; H, 4·9. Calc. for $C_{12}H_9Cl$: C, 76·4; H, 4·8%. [b] This *acid salt* had m. p. 90° (decomp.) (Found: C, 26·2; H, 1·2. $C_{10}H_5O_4N_2Cl_7$ requires C, 25·8; H, 1·1%).

(*b*) Aniline (5·0 g.), in trichloroacetic acid (26·0 g.) and water (20 c.c.), was diazotized as before. The solution was stirred for 24 hr. at 25° with benzene (250 c.c.) and afforded diphenyl (1·06 g.), m. p. and mixed m. p. 68—69°.

*Reaction of Toluene-*p*-diazonium Trifluoroacetate with Methyl Benzoate.*—(*a*) The acid salt (15·5 g.) was dissolved in methyl benzoate (140 c.c.). During ½ hr. the temperature was raised to 100° and after 2 hr. the excess of methyl benzoate was distilled off and the residue was distilled in steam. Part of the distillate solidified, and this was extracted and worked up in the usual way, to give *methyl 4-methyldiphenyl-4′-carboxylate* (0·13 g.), m. p. 115—116° (Found: C, 79·4; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%). After hydrolysis with aqueous-alcoholic sodium hydroxide, there was obtained the free acid, m. p. 245—248° (Found: C, 79·3; H, 5·9. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%), for which Carnelley (*J.*, 1877, **32**, 653) gave m. p. 245° (decomp.).

(*b*) *p*-Toluidine (3·20 g.) was diazotized as usual in trifluoroacetic acid (10·0 g.) and water (10 c.c.), with saturated aqueous sodium nitrite solution. Some solid salt separated, but was not removed. The slurry was stirred at 25° for 24 hr. with methyl benzoate (100 c.c.). Isolation as before yielded methyl 4-methyldiphenyl-4′-carboxylate (0·042 g.) m. p. 115—116°, undepressed on admixture with the material mentioned above.

*Reaction of Toluene-*p*-diazonium Trifluoroacetate with Toluene.*—(*a*) The acid salt (17·3 g.) and toluene (140 c.c.) were heated to 100° for 3 hr. After isolation as before, there was obtained 4 : 4′-dimethyldiphenyl (0·16 g.), m. p. 120—121° (Found : C, 92·4; H, 7·6. Calc. for $C_{14}H_{14}$: C, 92·3; H, 7·7%), for which Zincke (*Ber.*, 1871, **4**, 396) gave m. p. 121°.

(*b*) The suspension of toluene-*p*-diazonium acid trifluoroacetate obtained by diazotization with sodium nitrite of *p*-toluidine (2·14 g.) in trifluoroacetic acid (7·5 g.) and water (10 c.c. total) was stirred for 24 hr. at 25° with toluene (100 c.c.). 4 : 4′-Dimethyldiphenyl (0·045 g.), m. p. and mixed m. p. 119—121°, was obtained.

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The Chemistry of the Melanins. Part V. The Autoxidation of 5 : 6-Dihydroxyindoles.*

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The autoxidation of 5 : 6-dihydroxyindoles, which results in the formation of melanin-like pigments and hydrogen peroxide, has been examined by measurements of oxygen uptake, by elementary analysis of the pigments produced, and by spectroscopic studies of intermediates obtained by enzymic and silver oxide oxidation. With silver oxide yellow indole-5 : 6-quinones of varying degrees of stability were obtained. The results support the quinone polymerisation theory of melanin formation but there is evidence that some of the component indole units are more extensively oxidised.

EARLIER papers in this series have dealt with the synthesis of 5 : 6-dihydroxyindole and its derivatives, which were prepared with the object of comparing their behaviour on autoxidation and thus obtaining information about the mode of formation of the melanin-like product derived from 5 : 6-dihydroxyindole. As the work progressed (see, *e.g.*, Part IV *) it became clear that a qualitative and rather superficial comparison of the autoxidations was inadequate, and the experiments described in the present communication were developed in an effort to discover more objective methods. The autoxidations have been studied by measurements of oxygen uptake and of the absorption spectra of intermediates obtained by enzymic and silver oxide oxidations. Solubility and analytical data are recorded for the " melanins " produced in the autoxidations.

Oxygen Uptake and Hydrogen Peroxide Formation.—In preliminary measurements of oxygen uptake it was discovered that the buffer solution in which the dihydroxyindole had been oxidised contained appreciable amounts of hydrogen peroxide. In all subsequent experiments, therefore, the amount of oxygen absorbed by each indole and the amount of hydrogen peroxide produced at pH 7 and 8 were measured as described in the Experimental section. The results obtained are summarised in Table 1. Oxygen uptakes are calculated as moles of oxygen per mole of indole, and the peroxide formed is similarly expressed. The values in the column " Oxygen to polymer " represent uptakes corrected by subtracting the amount of oxygen consumed in peroxide formation. The variation of oxygen uptake with time at pH 8 is represented by sigmoid curves which indicate that the reactions are autocatalytic. The end of the induction period corresponds with the first appearance of colour in the solution.

The " oxygen to polymer " values of Table 1 are in reasonable agreement with values for the oxygen consumption involved in the conversion of 5 : 6-dihydroxyindole into melanin calculated from data presented by Duliere and Raper (*Biochem. J.*, 1930, **24**, 247) and by Mason (*J. Biol. Chem.*, 1947, **168**, 433) for enzyme-catalysed oxidations of tyrosine and

* Part IV, *J.*, 1951, 2426.

similar substrates. Any hydrogen peroxide formed in the enzymic oxidations would presumably be decomposed by the catalase present in the tyrosinase preparations.

The maximum rate of oxygen absorption by 5 : 6-dihydroxyindole at pH 8 was not materially affected by the addition of mushroom tyrosinase but the (apparent) induction period was reduced and the total amounts of oxygen absorbed and hydrogen peroxide

TABLE 1. *Oxygen consumption by 5 : 6-dihydroxyindoles.*

5 : 6-Dihydroxy-indole	O_2 uptake (moles)	H_2O_2 (moles)	Oxygen to polymer (moles)	Maximum rate (mole/min.)	O_2 uptake (moles)	H_2O_2 (moles)	Oxygen to polymer (moles)	Maximum rate (mole/min.)
	At pH 7.				*At* pH 8.			
Unsubstituted	1·31	0·46	1·08	0·020	1·38	0·52	1·12	0·110
1-Methyl	1·13 *	—	—	0·0056	1·41	0·36	1·23	0·021
2-Methyl	1·24	0·69	0·90	0·051	1·45	0·62	1·14	0·19
3-Methyl	1·22	0·79	0·83	0·093	1·27	0·58	0·98	0·45
2 : 3-Dimethyl	0·99	0·66	0·66	0·064	1·44	0·70	1·09	0·19
7-*n*-Propyl	1·12	0·67	0·79	0·021	1·42	0·60	1·12	0·091
3-Methyl-7-*n*-propyl	0·73	0·60	0·43	0·017	1·09	0·65	0·76	0·173
2 : 4 : 7-Trimethyl	1·43	0·48	1·19	0·075	1·67	0·46	1·44	0·382

* Oxygen was still being absorbed when experiment terminated.

TABLE 2. *Visible changes in autoxidations at* pH 8.

5 : 6-Dihydroxyindole	Intermediate colour	Final appearance
Unsubstituted	Purple	Black; black ppt.
1-Methyl	Yellow → pink → violet	Black; slight ppt.
2-Methyl	Brown	Black; black ppt.
3-Methyl	Blue	Intense dark blue; dark ppt.
2 : 3-Dimethyl	Brownish-purple	Almost black; no visible ppt.
7-Propyl	Purple	Black; no visible ppt.
3-Methyl-7-propyl	Blue	Dark blue; slight ppt.
2 : 4 : 7-Trimethyl	Red-purple	Intense red-brown; no visible ppt.

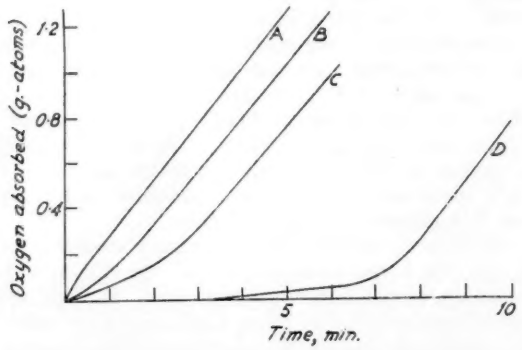


FIG. 1.

Curve	*Enzyme units*
A	5·0
B	2·5
C	1·0
D	nil

produced were also decreased, whilst the " oxygen to polymer " value remained virtually the same. When the reaction was carried out at various enzyme concentrations expressed as arbitrary enzyme units, the results shown in Fig. 1 were obtained. It appears that the enzyme has an effect on the *initial* rate of oxygen uptake which is roughly proportional to enzyme concentration but thereafter has little effect on the course of the reaction.

Visible changes in the autoxidising solutions at pH 8 (without enzyme) are summarised in Table 2. In every case except that of the 2 : 4 : 7-trimethylindole, filtration of the oxidised solution through a fine-mesh sintered funnel led to almost complete removal of the coloured products. The pigment from 5 : 6-dihydroxy-2 : 4 : 7-trimethylindole was obtained by acidification of the oxidised solution with dilute sulphuric acid.

Polymer yields and analytical data are collected in Table 3.

Spectrophotometric Experiments.—The formation of melanin from 3 : 4-dihydroxy-

phenylalanine (dopa) has been studied spectroscopically by Mason (*J. Biol. Chem.*, 1948, **172**, 83) who detected a purple intermediate characterised by a flat absorption maximum at 540 mμ. This result has now been confirmed with authentic 5 : 6-dihydroxyindole. When a solution of mushroom tyrosinase in phosphate buffer (pH 5·6) was added to a solution of the indole (*ca.* 5×10^{-5}M) in the same solvent, a purple colour developed which reached maximum intensity in approximately 20 minutes. The solution then showed an absorption maximum at 540 mμ (curve *A* in Fig. 2). It is interesting that an almost identical curve is obtained at pH 8, at which conversion into melanin is normally rapid. The

TABLE 3. *Polymer yields and analytical data.*[a]

5 : 6-Dihydroxyindole	Yield (% by wt.)	Composition (%) C	H	N	Atomic proportions C	H	O	N
Unsubstituted (A)	109	56·3	3·0	8·2	8·00	5·20	3·42	1·00
		56·6	3·1	8·2				
(B)	—	55·0	3·2	8·45	8·00	5·66	3·62	1·05
		55·2	3·3	8·45				
(C)	—	55·5	3·2	7·85	8·00	5·43	3·60	0·97
		55·8	3·1	7·8				
(D)	—	54·7	3·4	7·6	8·00	5·92	3·77	0·98
		54·5	3·3	8·0				
2-Methyl	93	56·1	3·8	7·3	9·00	7·36	3·95	1·00
3-Methyl	103	57·4	4·2	7·0	9·00	7·90	3·70	0·95
1-Methyl	102	55·4	4·0	—	9·00	7·78	4·09	1·00
2 : 3-Dimethyl	96	62·0	4·1	—	10·00	8·00	3·55	1·00
7-Propyl	—	62·0	5·1	—	11·00	10·85	3·55	1·00
3-Methyl-7-propyl	87	64·4	6·1	—	12·00	13·70	3·25	1·00

[a] The polymer samples had appreciable ash-contents (1—3%). The results have been calculated on an ash-free basis. [b] Expected C : N ratio assumed in calculation.

stability of the intermediate is probably a consequence of the very low concentrations used.

The nature of this intermediate is clearly of considerable importance and, in order to facilitate further discussion, the general trivial name *melanochrome* is suggested for the coloured compounds obtained by enzymic oxidation of dihydroxyindoles in very dilute solutions. Absorption curves for melanochromes derived from several dihydroxyindoles (at pH 5·6) are reproduced in Fig. 2.

The purple melanochrome obtained from 5 : 6-dihydroxyindole was regarded by Mason (*loc. cit.*) as being indole-5 : 6-quinone, but the position of its absorption is comparable with the maxima shown by the indolylbenzoquinones reported by Bu'Lock and Harley-Mason (*J.*, 1951, 703). In an attempt to detect monomeric quinones as intermediates in the formation of melanochromes, a study of the oxidation of dihydroxyindoles with silver oxide in a variety of solvents was made. In acetone solution all the indoles studied, except 5 : 6-dihydroxy-2-methylindole, gave evidence of a yellow intermediate, the stability of which varied considerably. In most cases the initially yellow solution rapidly became green and then blue or purple, changes which were catalysed by acids or bases, but with 5 : 6-dihydroxy-2 : 3-dimethylindole the yellow solution was stable for 20—30 minutes and the intermediate had a sharp absorption maximum at 362 mμ without appreciable absorption in the 500—600 mμ region (see Fig. 3, which also shows the very similar absorption curve of a solution obtained by silver oxide oxidation of 1 : 2 : 3 : 4-tetrahydro-6 : 7-dihydroxycarbazole).

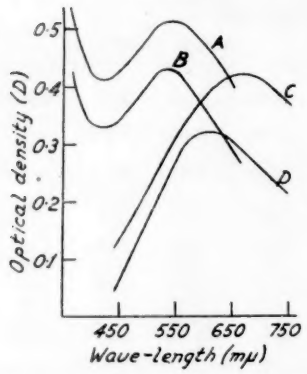
It seems likely that the yellow intermediates in the silver oxide oxidations are the true indole-5 : 6-quinones and that the more intensely coloured melanochromes are formed from them and are composed of a number, possibly a small number in some cases, of linked quinonoid indole molecules.

With 5 : 6-dihydroxy-2-methylindole a well-defined colour was not observed either in the enzymic or the silver oxide oxidations. In this case the oxidation may proceed so rapidly that the product is precipitated or perhaps absorbed by the oxidant. The behaviour of 5 : 6-dihydroxy-1-methylindole resembled that of 5 : 6-dihydroxyindole whilst the enzymic oxidation of 5 : 6-dihydroxy-2 : 3-dimethylindole gave a solution with an absorption maximum at *ca.* 445 mμ.

Absorption data for both types of oxidation are collected in Table 4.

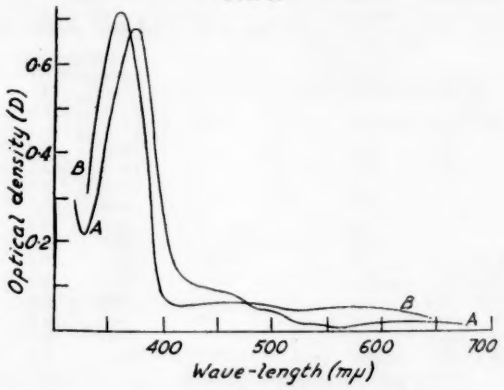
Solubilities of Synthetic Melanins.—Polymer samples were prepared at pH 8 as described in the Experimental section. It was found that the extent of drying had a marked effect on the solubility of the products; *e.g.*, samples dried in air were more soluble than samples which had been dried *in vacuo* for several days over phosphoric oxide. The results of qualitative solubility tests are given in Table 5.

FIG. 2.



Absorption spectra of melanochromes from: A, **5 : 6-dihydroxyindole**; *B*, **5 : 6-dihydroxy-7-n-propylindole**; *C*, **5 : 6-dihydroxy-3-methylindole**; *D*, **5 : 6-dihydroxy-3-methyl-7-n-propylindole**.

FIG. 3.



Absorption spectra of (*A*) **1 : 2 : 3 : 4-tetrahydrocarbazole-6 : 7-quinone** *and* (*B*) **2 : 3-dimethylindole-5 : 6-quinone**.

TABLE 4. *Spectroscopic data.*

5 : 6-Dihydroxyindole	Melanochrome : $\lambda_{max.}$ (mμ)	Silver oxide oxidation : $\lambda_{max.}$ (mμ)	5 : 6-Dihydroxyindole	Melanochrome : $\lambda_{max.}$ (mμ)	Silver oxide oxidation : $\lambda_{max.}$ (mμ)
Unsubstituted	540	510	3-Methyl	665	552
1-Methyl	540	523	3-Methyl-7-propyl	620	563
7-*n*-Propyl	535	515	2 : 3-Dimethyl	445	565 (final colour)

TABLE 5. *Polymer solubilities.*

5 : 6-Dihydroxyindole	Solubility of air-dried polymer in EtOH	Solubility of air-dried polymer in catechol	Solubility of intensively dried polymer in catechol
Unsubstituted	Insol.	Insol.	Insol.
1-Methyl	,,	Slightly sol.	,,
2-Methyl	,,	Insol.	,,
3-Methyl	Slightly sol.	Partially sol.	,,
2 : 3-Dimethyl	Insol.	Slightly sol.	,,
7-*n*-Propyl	Sol.	Sol.	Sol.
3-Methyl-7-*n*-propyl	Partially sol.	,,	,,
2 : 4 : 7-Trimethyl	Sol.	,,	,,

DISCUSSION

Consideration of the spectroscopic experiments described above suggests that the course of the autoxidation of **5 : 6-dihydroxyindole** may be represented as follows :

(Yellow) (Purple) (Black)

On this view, the melanochromes observed in the enzymic oxidations are polyindolequinones of the same type as, but less complex than, the insoluble melanins, the formation of which probably involves cross-linking of melanochrome chains.

The formation of considerable quantities of hydrogen peroxide in the autoxidation of each indole studied is presumably associated with the first reaction, *i.e.*, oxidation of indole to quinone. It is known, for example, that the autoxidation of duroquinol to duroquinone produces one mol. of hydrogen peroxide (James and Weissberger, *J. Amer. Chem. Soc.*, 1938, **60**, 98). The formation of the quinone almost certainly involves a free-radical reaction and, in this connection, it is interesting that the only significant effect of tyrosinase observed in this work is to eliminate the normal induction period. The possibility that hydrogen peroxide is derived in some way from an intermediate indoleninyl hydroperoxide analogous to the tetrahydrocarbazolyl peroxides (see Beer, Broadhurst, and Robertson, *J.*, 1952, 4946) has been rejected on the grounds that hydrogen peroxide is produced even in the autoxidation of 5 : 6-dihydroxy-1-methylindole, since *N*-substituted tetrahydrocarbazoles do not form hydroperoxides (*J.*, 1950, 2118).

By analogy with the autoxidation of duroquinol, one mole of peroxide should be produced per mole of indole.* The observed values (Table 1) vary between 0·36 and 0·79 mole and the difference between these values and the theoretical minimum of one mole must represent peroxide which has either decomposed to give oxygen or been utilised in some oxidation process. Recent work by Dr. Duxbury in these laboratories (*Chem. and Ind.*, 1953, 1364) suggests that hydrogen peroxide oxidation, possibly of the quinone but more probably of the polymerised material, is responsible for the formation of carbon dioxide observed by Clemo, Duxbury, and Swan (*J.*, 1952, 3464) in autoxidation experiments with 2-(3 : 4-dihydroxyphenyl)ethylamine and with 5 : 6-dihydroxyindole. It seems likely that carbon dioxide formation is *incidental* to the process of melanin formation (see Cromartie and Harley-Mason, *Chem. and Ind.*, 1953, 972) and cannot be regarded as strong evidence for the ring-fission hypothesis of melanogenesis (cf. Clemo *et al.*, *loc. cit.*; Jolles, *Chem. and Ind.*, 1953, 845) which therefore rests largely on analogy.

The analytical data for melanins obtained by autoxidation of 5 : 6-dihydroxyindole, given in Table 3, do not in fact indicate any striking change in the C : N ratio, and we conclude that melanins prepared under the conditions described are built up from C_8–N units derived from indole-5 : 6-quinone molecules. On this basis, the maximum oxygen uptake, corrected for hydrogen peroxide formation, should be two atoms. The "oxygen to polymer" values (see Table 1) for most of the dihydroxyindoles studied exceed the figure. For example, at pH 8, 5 : 6-dihydroxyindole and its 2-methyl derivative take up 2·2 and 2·3 atoms respectively and, if an appreciable amount of carbon dioxide is formed, these values would be smaller than the true uptakes. It appears, therefore, that, although the quinone polymerisation theory probably represents the main course of events, some other process involving consumption of oxygen occurs. This conclusion is supported by the analytical data (Table 3). The analyses of four independent samples of the melanin from 5 : 6-dihydroxyindole are surprisingly consistent if allowance is made for variation in water content (the correction is legitimate because the samples are hygroscopic when exhaustively dried). By subtraction of fractional amounts of water the empirical formulæ can be adjusted for comparison with the formula $(C_8H_3O_2N)_n$ expected on the basis of the polyindolequinone theory, and it then appears that the polymers contain approximately 0·3 atom of oxygen in excess of that required. This additional oxygen could be accommodated on the assumption that the melanins are essentially polyindolequinones in which some of the indole units are in a more highly oxidised state.

The mode of linkage of the quinone units remains to be discussed. Bu'Lock and Harley-Mason (*loc. cit.*) have argued, partly from the results of model experiments with indoles and quinones and partly on theoretical grounds, that the positions involved in the self-condensation of indole-5 : 6-quinone are the 3- and the 7-position. Our earlier observation that 5 : 6-dihydroxy-3-methylindole behaves differently from 5 : 6-dihydroxy-

* It is conceivable that hydrogen peroxide is also formed during the polymerisation stage since this must also involve oxidation of quinols, if the final product is to be largely quinonoid (cf. Bu'Lock and Harley-Mason, *loc. cit.*).

indole on autoxidation (Part II, *J.*, 1949, 2061) suggested that the 3-position was involved and the study of the spectra of melanochromes now reported supports this view. Enzymic oxidations of 5 : 6-dihydroxy-, 5 : 6-dihydroxy-1-methyl-, and 5 : 6-dihydroxy-7-*n*-propylindole gave spectroscopically similar intermediates ($\lambda_{max.}$ *ca.* 540 mμ) but compounds with a 3-methyl group and a free 2-position (5 : 6-dihydroxy-3-methyl- and 5 : 6-dihydroxy-3-methyl-7-*n*-propyl-indole) gave intermediates with maxima at longer wave-lengths (>600 mμ). The inference is clearly that 3-substitution, whilst not preventing the oxidative polymerisation, does deflect its normal course. The formation of a polymer of high molecular weight from 5 : 6-dihydroxyindole by a route involving the 3-position must, for the reasons advanced by Bu'Lock and Harley-Mason (*loc. cit.*), also involve the 7-position.

The 2-position in the indole nucleus shows some reactivity in the model condensations mentioned above and it seems probable that 5 : 6-dihydroxyindoles with a 3-methyl group and a free 2-position (activated by the adjacent alkyl group) will polymerise by linkage at the 2-position. In this case the steric limitations discussed by Bu'Lock and Harley-Mason no longer apply and the other position involved in polymer formation could be either the 4- or the 7-position. Judged by solubility properties (Table 5) the " polymer " obtained from 5 : 6-dihydroxy-7-*n*-propylindole at pH 8 is of lower molecular weight than that from the 3-methyl-7-*n*-propylindole. A possible explanation of this rather surprising result is that the dialkylindole contains an activated 2-position and can readily form a long-chain polymer linked at the 2- and the 4-positions, whereas with the 7-*n*-propylindole continued 3 : 4-linkage is prohibited for steric reasons and 2 : 4-linkage is difficult on account of the low reactivity of the 2-position. The pigment from 5 : 6-dihydroxy-7-*n*-propylindole should therefore be of low molecular weight.

This result conflicts with the recent report by Cromartie and Harley-Mason (*loc. cit.*) that an insoluble melanin-like pigment is obtained from 5 : 6-dihydroxy-7-methylindole by autoxidation at pH 6·85. These authors also state that autoxidation of 5 : 6-dihydroxy-2 : 3-dimethylindole gives an orange-red solution containing 2 : 3-dimethylindole-5 : 6-quinone which, in contrast to our results obtained at pH 8, is stable to further oxidation. Although the quinone from this indole is more stable than are those derived from other indoles, we find that autoxidation leads to a polymer which appears to be of considerable molecular weight. The polymer was not visible as a precipitate in the oxidised solution but could nevertheless be removed by filtration. The formation of an insoluble pigment from this indole implies that continued 4 : 7-linking of the indolequinone units is possible, and the light absorption of the corresponding melanochrome ($\lambda_{max.}$ *ca.* 445 mμ) might be explained on this basis. The colour finally produced in the silver oxide oxidation, however, appears to be quite anomalous.

Experimental

Oxygen Uptake and Hydrogen Peroxide Formation.—In a preliminary study of the autoxidation of 5 : 6-dihydroxyindole by Dr. A. G. White (see Part II, *J.*, 1949, 2062) some difficulty was experienced in obtaining reproducible results in oxygen-uptake experiments. This difficulty was not encountered in the present work for which the various hydroxyindoles, prepared by previously described methods, were rigorously purified, in most cases by vacuum-sublimation. With compounds containing a 2-methyl group, which did not sublime readily, repeated recrystallisation gave satisfactory results. Normal analytical-grade phosphates were used for the preparation of standard M/15-solutions (International Critical Tables, Vol. I, p. 81) which were mixed before each run to give buffers of the required pH.

The apparatus consisted of a tubular reaction vessel connected by small-bore pressure tubing to a gas-burette containing mercury. The reaction vessel and burette were kept at 25° by use of a thermostat and standard circulating arrangements. The reaction vessel was shaken vertically by a crank and eccentric at a speed sufficient to maintain the reaction mixture in a froth. The stopper of the vessel was a B19 standard cone carrying a small glass hook on which was suspended a small tube containing the dihydroxyindole. The system could thus be brought to equilibrium before the reaction was started by dislodging the tube.

Runs were normally carried out with 0·2 millimole of indole and 10 ml. of buffer solution. The reaction was followed by direct reading of the volume of the system at suitable intervals.

When oxygen uptake ceased the contents of the vessel were acidified with 2N-sulphuric acid (20 ml.), and the mixture was then filtered. Potassium iodide (1·0 g.) was added to the filtrate and after storage for 5 min. in the dark the liberated iodine was titrated with 0·01M-sodium thiosulphate. In a separate experiment with 5 : 6-dihydroxyindole the oxidising agent left in solution after the removal of pigment was shown to be hydrogen peroxide. Vacuum-distillation gave a colourless aqueous solution which reacted positively with acidified potassium iodide solution and with titanic sulphate, and was spectroscopically indistinguishable from distilled water in the range 300—700 mμ.

Polymer Yields and Analytical Samples.—The dihydroxyindoles (30 mg.) were introduced into the reaction vessel, the system was swept out with oxygen, the phosphate buffer (pH 8; 10 ml.) then added, and the vessel was shaken until no more oxygen was absorbed. Samples intended for analysis were collected by centrifugation, very thoroughly washed (25 times) in the centrifuge tube with distilled water, and then dried first *in vacuo* at room temperature over phosphoric oxide and finally to constant weight in a vacuum at 60°. In measurements of polymer yields the pigment was collected on a fine-mesh sintered crucible of known weight after acidification of the mixture with 2N-sulphuric acid (10 ml.) and was thoroughly washed and dried before weighing.

Silver Oxide Oxidations.—A solution of the dihydroxyindole (3—4 mg.) in pure acetone (5 ml.) was shaken with an excess of alkali-free silver oxide, and the suspension was then clarified by centrifugation. After 5 min., 1 ml. of the supernatant liquid was withdrawn and diluted to 25 ml. with acetone. The absorption spectrum of the resulting solution was measured.

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Picrotoxin and Tutin. Part VII. Experiments with Tutin.*

By J. R. FLETCHER, R. B. HALL, E. L. RICHARDS, S. N. SLATER, and C. C. WATSON.

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The infra-red spectra of tutin and its derivatives are described. Several isomerides of tutin are described and it is shown that the bromotutins are oxidised by chromic acid to the corresponding ketones.

THE close similarities between the molecular formulæ of picrotoxinin, $C_{15}H_{16}O_6$, and tutin, $C_{15}H_{18}O_6$, and between the behaviour of the two substances towards bromine and hydrogen, suggest some similarity in structure. Closer examination of tutin has now shown, however, a marked difference in function of the oxygen atoms. This was foreshadowed in Part IV (*J.*, 1952, 1042) where it was shown that tutin and dihydrotutin titrate as potentially monobasic substances under conditions where picrotoxinin and dihydropicrotoxinin titrate as potentially dibasic substances. This has now been correlated with significant differences in the infra-red spectra.

Picrotoxinin and its derivatives consistently show two absorption bands in the carbonyl region of spectra of the solid substances. All the tutin derivatives examined, however, show only one carbonyl band (see Table). Since tutin has no aldehydic or ketonic

Absorption spectra.

(Nujol pastes; bands moderate to strong, unless otherwise stated.)

	OH	CO	C:C		OH	CO
Tutin	3541, 3477	1772	1649	α-Bromotutin ...	3477	1776 (w)
*neo*Tutin	3488, 3425, 3355, 3280	1741	—	β-Bromotutin	3562, 3492, 3224	1773
β-Tutin	3344	1795	—	Bromo*iso*tutin ...	3470	1738
				Bromo*neo*tutin ...	3501	1793

properties and is potentially monobasic it may therefore be tentatively formulated as a monolactone. It cannot be a dilactone. There remain four oxygen atoms to be assigned functions. Tutin possesses four (Zerewitinoff) active hydrogen atoms, which suggests

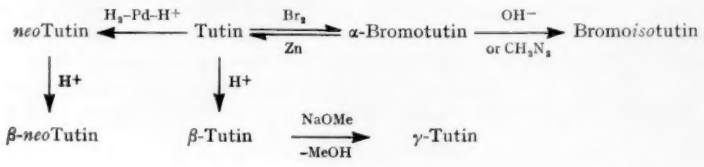
* Part VI, *J.*, 1952, 2292.

that possibly all four may be present as hydroxyl groups. Tutin forms a monoacetate, and *neo*tutin (see below) a diacetate; tutin reacts with two mols. of phenyl *iso*cyanate. This chemical evidence suggests a minimum of two hydroxyl groups. In the infra-red spectrum of tutin there are two bands in the 3-μ region. Of the bromotutins, α-bromotutin and bromo*iso*tutin (see below) have only one strong band in this region, but β-bromotutin has three well-resolved bands. *neo*Tutin has four strong bands in the 3-μ region. It seems clear that tutin is a polyhydroxy-compound, and that possibly all four unassigned oxygen atoms are present as hydroxyl groups. Unfortunately the substances of this series are not soluble in the preferred solvents and a proper evaluation of the solution spectra is therefore impossible.

As in the picrotoxinin series, the formation of monobromo-substitution products is accompanied by disappearance of the double bond. The conversion of α-bromotutin into an isomeride (now named bromo*iso*tutin) by alkali or diazomethane has already been described (Part IV, *loc. cit.*). β-Bromotutin, however, does not isomerise under these conditions. In this respect the bromotutins differ from the bromopicrotoxinins, both of which are affected (isomerisation and lactone opening) by alkali. Bromo*iso*tutin differs from all the known bromo-derivatives of both the picrotoxinin and the tutin series in being highly resistant to debromination, and the postulated *iso*tutin has not yet been prepared. We have, however, prepared *neo*tutin, the analogue of *neo*picrotoxinin. The existence of a " bromohydrotutin " isomeric with the two known bromotutins has already been established (Slater, *J.*, 1943, **50**, 143) and it was suggested that this substance was possibly derived from an isomer of tutin. With the isolation of *neo*picrotoxinin (Part III, *J.*, 1949, 806) it became evident that " bromohydrotutin " must be derived from a *neo*tutin, and we have now isolated such a substance directly from the complex mixture obtained on hydrogenation of tutin in the presence of palladium and mineral acid. In passing from picrotoxinin to *neo*picrotoxinin an acylatable hydroxyl group is generated. Tutin already contains an acylatable hydroxyl group and it was therefore not unexpected that *neo*tutin, $C_{15}H_{18}O_6$, should contain two such groups and form a diacetate. In the picrotoxinin series the change to the *neo*-structure results in the disappearance of the band at **6·06** μ, due to the terminal methylene group of the *iso*propenyl system of picrotoxinin, and this is paralleled by the loss of a similar band by tutin in passage to *neo*tutin. The terminal methylene group of tutin is confirmed chemically by the isolation of formaldehyde from the products of ozonolysis.

From the reaction mixture containing *neo*tutin a second substance, $C_{15}H_{20}O_6$, was isolated, isomeric with the dihydrotutin obtained on hydrogenation of tutin with a platinum catalyst, and with " β-dihydrotutin " (*J.*, 1943, 143). It forms a diacetate, suggesting a relation to *neo*tutin rather than tutin, and can in fact be obtained directly from the former by hydrogenation. It is therefore dihydro*neo*tutin. The nature of " β-dihydrotutin " has not yet been established but we have again observed its occurrence as the main isolatable constituent of the mixture obtained by prolonged hydrogenation of tutin with a palladium catalyst in the presence of mineral acid.

Although tutin is readily degraded by hot mineral acid, short heating with N-hydrochloric acid transforms it into a saturated isomer, a change which parallels the conversion of α-picrotoxinic acid into β-picrotoxinic acid. This substance, therefore termed β-tutin, is in turn isomerised by dilute methanolic sodium methoxide to γ-tutin. In a similar way *neo*tutin with acid forms the saturated β-*neo*tutin; the amount of the latter available did not suffice for us to determine whether a γ-*neo*tutin exists. Five isomers of tutin are thus now known, and a sixth has been isolated as its bromo-derivative. The relations between them are summarised in the annexed scheme.



Surprisingly, although α-bromotutin reacts with diazomethane, tutin itself is unaffected. However, if the *difference* in behaviour of these two reversibly related substances is emphasised, rather than the inertness of tutin, this parallels the *difference* in behaviour of the analogous pair, picrotoxinin and bromopicrotoxinin: picrotoxinin is converted into a derivative of picrotoxic acid, whereas bromopicrotoxinin is converted into a derivative of the very different α-picrotoxinic acid (Part VI, *J.*, 1952, 2292).

Both α- and β-bromotutin are oxidised by chromic acid to dehydro-derivatives, $C_{15}H_{15}O_6Br$, which, when debrominated yield the same substance, dehydrotutin, $C_{15}H_{16}O_6$. Although no carbonyl derivatives have been prepared from them, all three substances show carbonyl absorption in the ultra-violet and are clearly ketones derived from the corresponding secondary alcohols. Bromo*iso*tutin is likewise oxidised to bromodehydro*iso*tutin, which resists debromination by zinc. Dihydrotutin is oxidised by chromic acid to the corresponding ketone, $C_{15}H_{18}O_6$.

Experimental

M. p.s were observed on samples placed in a bath preheated to about 10° below the observed figures.

Reaction of Tutin with Phenyl iso*Cyanate*.—Tutin (220 mg.) was heated with phenyl *iso*cyanate (1 ml.) in a sealed tube at 100° for 20 hr. On cooling, the *bisphenylurethane* was deposited, and, crystallised from toluene–methanol and then toluene, had m. p. 175—177° (Found: C, 65·9; H, 5·6; N, 4·5. $C_{29}H_{28}O_8N_2$ requires C, 65·4; H, 5·3; N, 5·3%).

neo*Tutin*.—Palladous chloride (60 mg.) in hydrochloric acid (2 drops of concentrated acid in 4 ml. of water) was added to tutin (500 mg.) in ethanol (25 ml.) and shaken in hydrogen until the first rapid absorption had ceased. The resulting solution was concentrated to 3 ml., diluted with an equal volume of water, and set aside. Pure neo*tutin* separated as the hydrate (180 mg.), m. p. 108°, $[\alpha]_D^{18}$ +51·5° (in EtOH) (Found: C, 57·7; H, 6·6. $C_{15}H_{18}O_6,H_2O$ requires C, 57·7; H, 6·4%). Bromination yielded bromo*neo*tutin. The *diacetate* (from *neo*tutin, 100 mg., acetic anhydride, 0·6 ml., and pyridine, 0·3 ml.), crystallised from aqueous ethanol, had m. p. 168° [Found: C, 59·7; H, 5·8; Ac, 24·7. $C_{15}H_{16}O_6(CO{\cdot}CH_3)_2$ requires C, 60·3; H, 5·8; 2Ac, 22·8%].

*Dihydro*neo*tutin*.—(*a*) The aqueous mother-liquors from the above preparation slowly deposited crystals of *dihydroneotutin* (100 mg.), m. p. 240°, and finally after recrystallisation from water and then aqueous methanol, 277° (Found: C, 60·6; H, 6·45. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). (*b*) *neo*Tutin (60 mg.) in ethanol (25 ml.) in the presence of a palladium catalyst (palladous chloride, 30 mg., in water, 2 ml., and one drop of concentrated hydrochloric acid) was hydrogenated for 90 min. (52 c.c. taken up). The resulting solution, when reduced to small volume, deposited material (40 mg.) melting initially at *ca.* 200° and finally, after three crystallisations from water, at 276—277°. It showed no depression with the above specimen.

Dihydro*neo*tutin was recovered unchanged after further hydrogenation with a palladium catalyst for 22 hr. and did not react with diazomethane. The *diacetate* (from dihydro*neo*tutin, 60 mg., acetic anhydride, 1·5 ml., and pyridine, 0·3 ml.) crystallised from methanol and had m. p. 237° [Found: C, 60·1; H, 5·9; Ac, 24·8. $C_{15}H_{18}O_6(CO{\cdot}CH_3)_2$ requires C, 60·0; H, 6·3; 2Ac, 22·6%].

Ozonolysis of Tutin.—Tutin (250 mg.) in ethyl acetate (25 ml.) was ozonised (4 hr.), then evaporated *in vacuo*, and the residual ozonide was decomposed with water overnight. The aqueous solution was distilled to yield formaldehyde, isolated and identified as the dimedone derivative.

β-*Tutin*.—Tutin (2·5 g.) was heated with N-hydrochloric acid (85 ml.) at 100° for 35 min., giving a pale yellow solution. This was continuously extracted with ether (10 hr.), and the extract distilled, to give a residual oil which rapidly deposited crystals which, recrystallised from ethanol, had m. p. 255—258° (Found: C, 61·0; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·3; H, 6·1%). β-*Tutin* is stable to bromine water and cold dilute alkaline permanganate. It reduces hot sensitised ammoniacal silver nitrate. It is rapidly decomposed by hot 1 : 1 hydrochloric acid.

γ-*Tutin*.—β-Tutin (80 mg.) in methanol (15 ml.) containing sodium methoxide (0·5 ml.; M/15) was set aside for 2 days and then acidified with glacial acetic acid (1 drop), evaporated *in vacuo*, and crystallised from methanol. γ-*Tutin* had m. p. 240° (Found: C, 60·9; H, 6·1%).

It was also obtained by treating β-tutin in methanol with ethereal diazomethane and adding one drop of 2N-sodium hydroxide.

β-neo*Tutin.*—*neo*Tutin was heated for a short period with excess of mineral acid (*ca.* N). The solution rapidly became yellow. The product was continuously extracted with ether, from which a crystalline material separated. This was recrystallised from ether (in which it is nearly insoluble) with the aid of an extraction thimble, giving β-neo*tutin*, m. p. 270° (Found : C, 61·9; H, 6·45%).

α-*Bromodehydrotutin.*—α-Bromotutin (250 mg.) in the minimum quantity of glacial acetic acid was mixed with a saturated solution of chromic acid (750 mg.) in glacial acetic acid. The mixture was set aside overnight, diluted with five volumes of water, and shaken. A crystalline precipitate rapidly formed (195 mg.). The *dehydro*-derivative crystallised from aqueous ethanol in small cubes, m. p. 174—175° (Found : C, 48·3; H, 4·0; Br, 21·3. $C_{15}H_{15}O_6Br$ requires C, 48·5; H, 4·1; Br, 21·6%), $\lambda_{max.}$ 296 mμ (log ε 1·41 in EtOH).

β-*Bromodehydrotutin.*—Oxidation of β-bromotutin (100 mg.) with chromic acid (300 as mg.) above yielded 43 mg. of crude *ketone*, m. p. 130°. It was crystallised six times from ethanol and finally obtained as small cubes, m. p. 210° (Found : C, 48·4; H, 4·25%), $\lambda_{max.}$ 304 mμ (log ε 1·44 in EtOH).

*Bromodehydro*iso*tutin.*—Bromo*iso*tutin (100 mg.) with chromic acid (300 mg.) as above yielded 95 mg. of crystalline *ketone*. Recrystallised from ethanol–dioxan it formed long needles, m. p. 280° (Found : C, 48·2; H, 4·25; Br, 21·0%), $\lambda_{max.}$ 314 mμ (log ε 1·8 in EtOH).

Dehydrotutin.—α-Bromodehydrotutin (60 mg.) in ethanol (3 ml.) was reduced at the b. p. with zinc dust (300 mg.), added gradually, followed by the addition of 15 drops of dilute acetic acid. The product was filtered and cooled. *Dehydrotutin* (30 mg.) separated in long needles and, recrystallised from ethanol, had m. p. 245° (Found : C, 61·4; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%), $\lambda_{max.}$ 304 mμ (log ε 1·57 in EtOH).

β-Bromodehydrotutin, debrominated in the same way, yielded the same material (m. p. and mixed m. p.).

Oxidation of Dihydrotutin.—Dihydrotutin (250 mg.), oxidised as above with chromic acid (600 mg.), yielded a crystalline product (75 mg.) which recrystallised from ethanol as long flat needles, m. p. 259—260° (decomp.) (Found : C, 60·8; H, 5·75. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%). A further quantity (40 mg.) of the *ketone* was obtained by treating the diluted acetic acid solution with a slight excess of barium acetate, filtering, and extracting the filtrate continuously with ether for 6 hr. It had $\lambda_{max.}$ 299 mμ (log ε 1·52 in EtOH).

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The Preparation and Physical Properties of Pure Pyridine and Some Methyl Homologues.

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The methods used in the preparation from commercially available material of samples of pyridine, α-, β-, and γ-picoline, and 2 : 6-lutidine of purity greater than 99·7 moles % are described. The purities of the samples have been established by freezing-point measurements, and the freezing points, cryoscopic constants, and latent heats of fusion of the 100% pure bases have been computed. The normal boiling points have been measured with a standard deviation of less than ±0·005°. The pressure coefficients of the boiling points and the latent heats of vaporization are also placed on record. The densities of anhydrous base samples at 20° and at 30° have been measured and the coefficients of cubical expansion at 25° have been derived. The refractive indices for the *C*, D_1, *e*, and *F* lines of the anhydrous bases at 20° have been found and fitted to a modified Hartmann equation : $n = n_\infty + C/(\lambda - \lambda^*)^{1\cdot6}$. The molar refractivities have also been calculated. The infra-red spectra of the highly purified base samples in the liquid and vapour states have been measured for the wave-length range 2—15 μ.

Pyridine and its methyl homologues would offer a wide scope for studies of the relation between structure and properties but for the inaccessibility of many members of the series. The technical interest which, however, now attaches to certain of the homologues prompted an undertaking of various physico-chemical measurements, for which there would ultimately be required substantial quantities of all the homologues. Some of the physico-chemical measurements made in this laboratory on the more readily accessible bases have already been placed on record : vapour pressures, Herington and Martin, *Trans. Faraday Soc.*, 1953, **49**, 154; solubilities in water and in D_2O, Andon and Cox, *J.*, 1952, 4601, Cox, *ibid.*, p. 4606; ultra-violet absorption spectra and dissociation constants, Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26; and heats of formation, Cox, Challoner, and Meetham, *J.*, 1954, 265; and others are in progress. Since one of the main purposes in this programme was the critical assessment of existing physico-chemical data, it is clear that the final purification and the quantitative estimation of residual impurity are crucial. It is, indeed, particularly true that discrepant and erroneous statements on the physical and chemical properties of individual bases in this series have been the result of observations on impure materials. This paper therefore presents work on the purification of pyridine, the three isomeric picolines, and 2 : 6-lutidine, and on the measurement of some salient physical properties.

These five bases, separated from coal tar or crude benzole fractions, are available in commercial grades of various qualities. The purity of the best of these, " Pyridine A.R.," is above 99% ; that of the others such as β- or γ-picoline may be as low as 95%. The standard of purity we set ourselves, *ca.* 99·9 moles % as deduced from the freezing- or melting-point curve, proved very difficult to achieve, even from the best grades of starting material, because (*a*) small amounts of pyrrole derivatives, sulphur compounds, hydrocarbons, and phenols may be present, (*b*) some homologues, *e.g.*, β- and γ-picoline, have very similar boiling points, and (*c*) the bases are hygroscopic. Thus it was first necessary to remove non-basic contaminants. Further treatment consisted of two or all of the processes, distillation (fractional or azeotropic), fractional crystallization from a melt, and crystallization of a suitable complex compound.

The following properties have now been measured or computed, collated with published values, and placed on record : freezing points, latent heats of fusion, and cryoscopic constants (Table 2); boiling points, pressure coefficients of boiling point, and latent heats of vaporization (Table 3); densities at 20° and at 30°, and coefficients of cubical expansion at 25° (Table 4); refractive indices for the *C*, D_1, *e*, and *F* lines at 20°, and molar refractivities for the D_1 line (Figs. 2—6, Table 5); and infra-red absorption spectra (2—15 μ)

for the liquids (Table 7). They include the properties likely to be of greatest use in the characterization of specimens of these bases and in setting up analytical techniques. The thermal data are also of interest to chemical engineers.

Experimental

Purification of Individual Bases.—Pyridine. This base has no homologues of similar b. p., so fractional distillation is effective for preliminary purification (Heap, Jones, and Speakman, *J. Amer. Chem. Soc.*, 1921, **43**, 1936; Wilkie and Shaw, *J. Soc. Chem. Ind.*, 1927, **46**, 469T; Carignan and Kraus, *J. Amer. Chem. Soc.*, 1949, **71**, 2983). But we found that even repeated distillation, in a column of 50-plate efficiency, of commercial pyridine of the best quality did not suffice.

Other processes of purification which have been used are : crystallization of the zinc chloride complex (Carignan and Kraus, *loc. cit.*) ; crystallization of the perchlorate (Arndt and Nachtwey, *Ber.*, 1926, **59**, 448) and of the hydrogen oxalate (Rozhdestvenskiĭ, Pukirev, and Maslova, *Trans. Inst. Pure Chem. Reagents, U.S.S.R.*, 1935, No. **14**, p. 58) ; and combination of fractional freezing with distillation (Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79). In some of these cases the products were dried, but there is no record of any previous attempt to estimate the residual moisture or to evaluate the total molar percentage of residual impurities from freezing-point behaviour.

To remove non-basic, particularly sulphur-containing, contaminants (Coulson and Ditcham, *J. Appl. Chem.*, 1952, **2**, 236) steam was passed through a boiling solution of the base in 1·2 equivs. of 22·6% sulphuric acid until about 10% of the pyridine had been carried off along with contaminating substances. Base was then liberated by an excess of concentrated aqueous sodium hydroxide, separated, and dried over solid sodium hydroxide. Fractional distillation through a 50-plate Stedman gauze-packed column (reflux ratio 50 : 1) gave a fraction of b. p. 93·7—94·0°/400 mm. and purity 99·5 moles % (f.-p. curve). The main residual impurity was water, it being difficult to avoid atmospheric contamination. Infra-red spectroscopy (Coulson, Hales, and Herington, *J.*, 1951, 2125) was capable of detecting 0·002% by vol. (0·01 mole %) of water in pyridine, and up to 0·5 mole % of water was found in samples obtained as above. The best specimen had a purity of 99·85 ± 0·03 moles % (f.-p. curve) and was obtained by subjecting the 99·5% sample to fractional freezing and then simple distillation to remove water and tap-grease. By the use of a Dewar vessel, the exhaustion of which could be varied at will, the base was cooled at a controlled rate to a temperature just below the f. p. and allowed to crystallize slowly until about one-tenth remained liquid. The liquid was then drawn off and the crystals were melted and the process was repeated a number of times, all in a closed apparatus. The purified base was then transferred to a thoroughly dry all-glass still and about 25% was slowly distilled off. Distillation of the residue gave the best specimen. A specimen of 99·87 moles % purity was obtained by adding about 10% of pure benzene (cf. Berg, Harrison, and Montgomery, *Ind. Eng. Chem.*, 1945, **37**, 585) to the 99·5% material and fractionally distilling it through a 50-plate Stedman column, a forecut containing water and benzene being taken off and a bulk fraction of b. p. 93·7—94·0°/400 mm. being collected. The latter, although very dry, contained benzene and when diluted with a large volume of water became cloudy : it was therefore not used for the physical measurements.

α-Picoline. α-Picoline also can be purified considerably by fractional distillation (Wilkie and Shaw, *J. Soc. Chem. Ind.*, 1927, **46**, 469T; Hoffman and VanderWerf, *J. Amer. Chem. Soc.*, 1946, **68**, 997; Freiser and Glowacki, *ibid.*, 1948, **70**, 2575). When a commercial specimen of " pure " α-picoline in aqueous sulphuric acid was treated with steam as above, a small amount of a mixture of xylenes (chiefly *m*- and *p*-) was found in the condensate. The remaining purification and the drying were the same as for pyridine, and the best specimen had 99·87 ± 0·01 moles % purity (f.-p. curve). When α-picoline is supercooled it crystallizes in an unstable form melting about 0·13° below the stable form, and care must be taken to seed the liquid with the stable form when the f.-p.–time curve is plotted for purity determination.

The only previous determination of the purity of a purified α-picoline (99·85 moles %) is that of Freiser and Glowacki (*loc. cit.*) who also noted the two crystalline forms. The residual impurity in their specimen, as in ours, was mainly water (Coulson, Hales, and Herington, *loc. cit.*).

β-Picoline. The main source of difficulty in the preparation of β-picoline is its natural association, in coal tar, with γ-picoline and 2 : 6-lutidine which have b. p.s extremely close to,

and on either side of, that of β-picoline. The separation and purification of these compounds were studied by Coulson and Jones (*J. Soc. Chem. Ind.*, 1946, **65**, 169; B.P. 585,108, 598,036, 602,273). Many methods of separation have been suggested more recently, but, although they have all been used to prepare concentrates, very few have been applied to the preparation of the three bases in pure states (see, however, Hoffman and VanderWerf, *J. Amer. Chem. Soc.*, 1946, **68**, 997; Brown and Barbaras, *ibid.*, 1947, **69**, 1137; Johnson, *J.*, 1947, 1626; Angyal, *J. Proc. Austral. Chem. Inst.*, 1947, **14**, 12; Riethof, Richards, Savitt, and Othmer, *Ind. Eng. Chem. Anal.*, 1946, **18**, 458; Glowacki, Winans, and Koppers Co., U.S.P. 2,402,158). We did not find the method of Riethof, Richards, Savitt, and Othmer, (*loc. cit.*; reaction with acetic and phthalic anhydride) to be as specific as claimed, and we were not able to prepare β-picoline, by this or any other method, which did not react to some extent with phthalic and acetic anhydrides. The purity of a specimen, originally 96%, was not raised beyond 99% by exhaustive treatment with the anhydrides.

We found that the most convenient separation of pure β-picoline from commercial coal-tar materials involved the following steps. After removal of non-basic contaminants, as for pyridine, cruder specimens (30—90% of β-picoline) were treated with urea for removal of 2 : 6-lutidine. β-Picoline so obtained (90% or purer) was then azeotropically fractionated with acetic acid (Coulson and Jones, *loc. cit.*). The base recovered from the azeotrope, b. p. 114·5°/212 mm., by treatment with excess of 30% aqueous sodium hydroxide, was dried over solid sodium hydroxide and then by very slowly distilling off a small amount, in which water was removed, until the b. p. was constant. This base had 96% purity and was suitable for fractional freezing. It was then kept at such a temperature that at least 24 hr. were required, after seeding, before about 90—95% was frozen. The liquid was poured off, the crystals were melted, and the process was repeated 5—6 times or until an examination of the f.-p. curve showed that the required purity had been reached. The best sample of β-picoline so secured was dried by slowly distilling off a forecut, and had 99·97 ± 0·02 moles % purity.

γ-Picoline. Pure γ-picoline, from commercially available specimens (90—95%) or from a β-picoline cut (*ca.* 30%), was prepared similarly to the β-isomeride. Non-basic material was removed, then 2 : 6-lutidine, if necessary, through the urea complex. Next the purity was raised to 98% by azeotropic fractionation, the acetic acid azeotrope being collected at 116·5—117°/212 mm., and finally a best sample (99·88 ± 0·02 moles %) was secured by slow fractional freezing at temperatures close to the m. p. of the pure base.

2 : 6-*Lutidine.* Pure 2 : 6-lutidine was separated from three sources, two being commercial specimens of the base, and the third a typical " β-picoline cut " of tar bases, from which pure β- and γ-picolines were also separated. In each case non-basic contaminants were removed first. It was not difficult by azeotropic fractionation (Coulson and Jones, *loc. cit.*) to raise the purity of 2 : 6-lutidine from all these sources to 95 moles %, but fractional freezing did not then prove economical. Crystallisation of the urea complex (Riethof and Pittsburgh Coke and Iron Co., B.P. 592,384; U.S.P. 2,383,016, 2,295,606) was very effective either for the concentration of 2 : 6-lutidine or for raising the purity of 90—95% material to 99 moles %, beyond which fractional freezing is preferable.

The best procedure was as follows. To a mixture of 450 g. of water and 527 g. of urea there was added 470 g. of commercial 2 : 6-lutidine or an equivalent amount of a picoline cut. After being heated under reflux until two liquid layers were obtained and no solid remained undissolved, the mixture was cooled, with stirring, whereupon the complex crystallized. It was filtered off and added to 450 g. of water, and the whole was warmed until no solid remained, then stirred and cooled to induce crystallization. After a second recrystallization from 450 g. of water, the purified complex was boiled for 6 hr. under reflux with sodium hydroxide (500 g.) in water (1150 g.). When the liquid was cooled, regenerated 2 : 6-lutidine separated. It was removed, dried (NaOH), and distilled. The yield was 78% of material of purity *ca.* 99 moles %. Base recovered from the filtrates was worked up for β- and γ-picolines.

The best sample of 2 : 6-lutidine was obtained by slow fractional freezing of the 99% material, followed by a final distillation. Its purity was 99·89 ± 0·01 moles %.

Examination of Purified Bases for Particular Impurities.—Pyrrole. None of the five pure bases, in the form of its hydrochloride, gave a detectable colour with *p*-dimethylaminobenzaldehyde; each therefore contains less than 1 p.p.m. (0·0001 mole %) of pyrrole or pyrrole homologue, which is the limit of the sensitivity of this test in the presence of these pyridine bases.

Sulphur. The sulphur contents, determined by combustion, were all less than 0·003 mole %.

Physico-chemical Measurements.—Freezing points, latent heats of fusion, cryoscopic constants,

and the quantitative estimation of purity. The cryoscopic technique was determined by the extreme hygroscopicity, the need to add known amounts of impurity (as cryoscopic constants were unknown), and the need for economy of material. A 20-ml. sample was placed in the apparatus described by Herington and Handley (*J.*, 1950, 199), a thermocouple being used in place of the thermistor. One junction was placed in a triple-point water cell and the measurements of e.m.f. were made with a Tinsley three-dial vernier potentiometer. Readings were obtained on the last dial to 1 μv and values to the nearest 0·05 μv were obtained by interpolation from the galvanometer deflections.

A very general method of calculating the purity and the freezing-point constants of a material from the behaviour of samples during freezing is discussed by Schwab and Wichers (" Temperature. Its Measurement and Control in Science and Industry," Reinhold Publ. Corp., New York, 1941, p. 256), and a modified form of this was employed. A great advantage is that the rate of crystallization need not be assumed to remain constant throughout the freezing period. One assumes merely that the same fraction of solid is formed at equal fractions of the total freezing time in experiments with and without added impurity, and this can be checked by repeating the experiment after the addition of a second portion of impurity.

The technique was therefore as follows. A curve of temperature against time was obtained for a purified sample of base and the experiment was then repeated under the same conditions after the addition of a known amount of impurity. *iso*Octane was employed as impurity because it was thought that this would not form mixed crystals with the base; this was confirmed for pyridine, whose latent heat of fusion calculated from the results obtained by the use of *iso*octane agreed with the best published values. The data obtainable from these two curves alone are sufficient to calculate the cryoscopic constant, the purity of the sample, and the f. p. of the 100% pure base, but the experiment was repeated after the addition of a further

TABLE 1. *Pyridine. Temperatures are given in terms of the e.m.f.* (μv) *of the thermocouple.*

	Initial f. p. (t_f)	Depression (y) by impurity	Δt	Change in Δt produced by impurity
Original sample	1444·0	—	1·7°	
After the addition of 0·318 mole % of *iso*octane ($x_1 = 0·318$)	1450·05	6·05	3·5	1·8°
After the addition of 0·605 mole % of *iso*octane ($x_1 = 0·605$)	1456·45	12·45	5·65	3·95

quantity of *iso*octane. Table 1 summarises a typical experiment. The time for complete freezing was determined by graphical analysis (see, for example, Stull, *Ind. Eng. Chem. Anal.*, 1946, **18**, 234), and the initial f. p. of the actual sample (t_f) was also estimated from such a plot. The values of y being proportional to x_1, the depression θ (°c) of the initial f. p. produced by 1 mole % of impurity, is readily calculated, the calibration of the thermocouple being used to convert μv into °c. From the value of θ so obtained and the f. p. of the 100% material (see below), the cryoscopic constant, K_f, and the latent heat of fusion can be calculated. Each value of Δt (μv) corresponds to the difference between the initial f. p. and the freezing temperature at a time equal to half that required for complete freezing. The changes in Δt produced by added impurity (column 5, Table 1) are proportional to the amounts of added impurity but corresponding values in columns 3 and 5 are not equal; it follows that not exactly half the charge is frozen at a time equal to half that required for complete freezing, and hence that the mathematical analysis of the curves advanced by Rossini *et al.* (*J. Res. Nat. Bur. Stand.*, 1941, **26**, 591; 1944, **32**, 197) cannot be employed with the present results. In particular the thermocouple e.m.f. corresponding to the f. p. of the 100% pure material cannot be obtained by simply subtracting the value (1·7) given for the original sample from that in column 2. When the conditions shown in Table 1 exist, the number of microvolts which must be subtracted from the e.m.f. corresponding to the initial f. p. of the original sample to obtain the e.m.f. corresponding to the f. p. of the 100% pure pyridine base, is given by $y\Delta t_1/(\Delta t_2 - \Delta t_1)$, where Δt_1 and Δt_2 refer respectively to observations before and after addition of impurity. For a material (*e.g.*, γ-picoline) which freezes above +0·010° the value of $y\Delta t_1/(\Delta t_2 - \Delta t_1)$ must be added instead of subtracted, to yield the thermocouple e.m.f. corresponding to the f. p. of the 100% pure material. The molar percentage (x) of impurity in the original sample is given by the expression $x_1\Delta t_1/(\Delta t_2 - \Delta t_1)$ where x_1 is the molar percentage of added impurity. The initial f. p. of the actual sample expressed on the International Temperature Scale (t_f) was obtained by calibrating the thermocouple directly after use against a platinum resistance thermometer at very nearly the temperature under investigation.

Curves were determined twice for each value of x_1. The derived quantities θ, x, and $t_{f,0}$ (the f. p. of 100% pure material) were calculated from the mean values of y, Δt_1, and Δt_2. The standard deviations of θ, x, and $t_{f,0}$ were also calculated, the errors arising from uncertainties in x_1 being neglected, *i.e.* from $\sigma_\theta^2 = (\sigma_{t,f}^2 + \sigma_{t,2}^2)/x_1^2$, where $\sigma_{t,f}$ and $\sigma_{t,2}$ are the standard deviations of the mean initial f. p. of the original sample, and of the mean initial f. p. after the addition of x_1 moles % of impurity. The separate values of θ so obtained were then treated as if they were independent determinations and were combined to give a grand mean and standard deviation, each value of θ being weighted by the appropriate σ_θ^{-2} term. The final results so obtained are listed in Table 2.

TABLE 2. *Freezing constants for pyridine, α-, β-, and γ-picoline, and 2 : 6-lutidine.*

	Purity ($100 - x$) moles %	Depression (θ) produced by 1 mole % of impurity	Depression (K_f) for 1 mole of impurity in 1000 g.	Latent heat of fusion (l_f, cal./g.)	F. p. of sample (t_f)	F. p. for 100% purity ($t_{f,0}$)
Pyridine	99·73	0·607°	4·75°	22·4	−41·71°	−41·55°
	±0·03	±0·017°	±0·13°	±0·6	±0·04°	±0·05°
α-Picoline ...	99·83	0·365	3·36	25·2	−66·81	−66·74
	±0·01	±0·060	±0·55	±4·1	±0·04	±0·04
β-Picoline ...	99·89	0·529	4·88	26·5	−18·25	−18·20
	±0·02	±0·015	±0·14	±0·8	±0·04	±0·04
γ-Picoline ...	99·88	0·557	5·13	29·7	+3·58	+3·65
	±0·02	±0·029	±0·27	±1·7	±0·04	±0·04
2 : 6-Lutidine	99·89	0·596	6·32	22·4	−6·16	−6·10
	±0·01	±0·026	±0·28	±1·0	±0·04	±0·04

The cryoscopic constants, K_f, were then calculated from these grand mean values of θ, and the standard deviations, $\sigma_{K,f}$, of K_f were derived from the expression $K_f\sigma_\theta/\theta$. The latent heats of fusion were obtained by means of the expression $\boldsymbol{R}T_{f,0}^2/1000K_f$, where $T_{f,0}$ is $t_{f,0}$ converted into degrees Kelvin, and their standard deviations, $\sigma_{l,f}$, were computed by the equation $\sigma_{l,f} = l_f\sigma_{K,f}/K_f$.

The standard deviation, σ_x, of each experimentally determined value of x was calculated by the equation

$$\sigma_x^2 = x_1^2[\sigma_{\Delta t,1}^2(\Delta t_2)^2 + \sigma_{\Delta t,2}^2(\Delta t_1)^2]/(\Delta t_2 - \Delta t_1)^4$$

where $\sigma_{\Delta t,1}$ and $\sigma_{\Delta t,2}$ are the standard deviations of the mean values of Δt_1 and Δt_2 respectively. The experimentally determined values of x were then treated as if they were independent determinations and were combined into grand means by weighting each value by the appropriate σ_x^{-2} term. The purities in moles % ($100 - x$) so obtained are listed in Table 2.

The f. p. of 100% pure material was calculated by the equation $t_{f,0} = t_f + \theta x$, the grand mean values of θ and x (Table 2) being used and t_f being the initial f. p. of the actual sample. The standard deviation, $\sigma_{t,f,0}$, of $t_{f,0}$ was calculated from the expression $\sigma_{t,f,0}^2 = \sigma_{t,f}^2 + x^2\sigma_\theta^2 + \theta^2\sigma_x^2$. The standard deviation, $\sigma_{t,f}$, arises from errors in the measurement and extrapolation to zero time of the thermocouple e.m.f., and in its conversion into degrees Celsius. On the basis of a number of measurements an overall standard deviation of 0·04° has been ascribed to t_f.

It is considered, however, that the value of $t_{f,0}$ for α-picoline may not be quite so accurate as the value of $\sigma_{t,f,0}$ suggests, because of the difficulties attendant on the existence of two crystalline forms.

The literature contains 28 values for pyridine ranging from −100° to −37·5°, 5 for α-picoline from −69·9° to −64°, 4 for β-picoline from −20·8° to −17·7°, 4 for γ-picoline from 1·6° to 4·3°, and 4 for 2 : 6-lutidine from −6·3° to −5·5°. However, except for a single value for α-picoline (−66·55° ±0·08°; Freiser and Glowacki, *J. Amer. Chem. Soc.*, 1948, **70**, 2575) all the published values are for actual samples of unestablished purity.

The latent heat of fusion of pyridine in Table 2 agrees with that (21·8 ± 0·4 cal./g.) calculated from Beckmann and Waentig's results (*Z. anorg. Chem.*, 1910, **67**, 17), and is slightly less than that (24·99 cal./g.), measured calorimetrically by Parks, Todd, and Moore (*J. Amer. Chem. Soc.*, 1936, **58**, 398). It is considerably greater than the value (9·4 cal./g.) reported by Pearce and Bakke (*Iowa Acad. Sci.*, 1946, **43**, 171), which appears to be seriously in error. The latent heat of fusion of α-picoline now reported is not very accurate because of the difficulties mentioned above, but is in reasonable agreement with a value (21 cal./g.) calculated from the results of Freiser and Glowacki (*loc. cit.*), although not with that (12·9 cal./g.) of Lemmerman, Davidson, and

VanderWerf (*J. Amer. Chem. Soc.*, 1946, **68**, 1361). The values for the latent heats of fusion of β- and of γ-picoline are also not in good agreement with the last-mentioned workers' results (20·3 cal./g. and 23·7 cal./g. respectively).

Normal boiling points, values of $(dt/dp)_{760\ mm.}$ *and latent heats of vaporization.* The normal boiling points, values of $(dt/dp)_{760\ mm.}$, and the heats of vaporization of samples of bases purified as here described have recently been computed from vapour pressure–temperature measurements (Herington and Martin, *Trans. Faraday Soc.*, 1953, **49**, 154), and are given in Table 3. The latent heats of vaporization are uncorrected for deviations of the vapours from the ideal gas laws and the molal volume of the liquid has been neglected in these calculations. The latent heats of vaporization at the normal boiling points were calculated by using the constants of the Antoine equation which had been fitted to the experimental vapour-pressure data over a large temperature range.

TABLE 3. *Normal boiling points,* $(dt/dp)_{760\ mm.}$, *and latent heats of vaporization.*

Compound	B. p. at 760 mm.	$(dt/dp)_{760\ mm.}$ (° c/mm.)	Latent heat of vaporization at 760 mm. (cal./g.)
Pyridine	115·256° ± 0·002°	0·04535	109·95 ± 0·04
α-Picoline	129·408 ± 0·004	0·04695	96·92 ± 0·04
β-Picoline	144·143 ± 0·003	0·04873	100·34 ± 0·04
γ-Picoline	145·356 ± 0·002	0·04887	100·61 ± 0·03
2 : 6-Lutidine	144·045 ± 0·003	0·04818	88·16 ± 0·03

Approximately 70 determinations of the normal b. p. of pyridine have been reported, the more recent values varying almost as much as those reported before 1900, *e.g.*, from 113° (Kennard and McCusker, *J. Amer. Chem. Soc.*, 1948, **70**, 3375) to 115·5—115·8° (Corey, *ibid.*, 1953, **75**, 1172). The new value (Table 3) agrees within 0·01° with a value (115·26°) ascribed by Timmermans ("Physico-Chemical Constants of Pure Organic Compounds," Elsevier Publishing Co., New York, 1950) to Hoffman and VanderWerf (*ibid.*, 1946, **68**, 997). They, however, give only 114·1°/730 mm. The new value differs by as much as 0·11—0·32° from other values selected by Timmermans (*op. cit.*).

The normal b. p. of α-picoline obtained agrees with that reported by Freiser and Glowacki (*loc. cit.*) within the accuracy claimed by those workers (rather better than 0·1°), but differs considerably from the other values selected by Timmermans (*op. cit.*).

The values of $(dt/dp)_{760\ mm.}$ in Table 3 for pyridine and for α-picoline are rather greater than those quoted by Timmermans.

The latent heats of vaporization determined from the vapour pressures, by assuming the ideal gas laws, should exceed the latent heats of vaporization determined calorimetrically by an amount equal to $0{\cdot}0318657[(B - V_L)T]/(dt/dp)$ cal./mole, where B is the second virial coefficient of the vapour, V_L is the molal volume of the liquid at the b. p., and (dt/dp) is expressed in degrees Celsius per mm. of mercury. Since B is negative and V_L is positive it follows that the values in column 4, Table 3, should be numerically greater than the calorimetric values. Five calorimetric measurements have been reported for pyridine, ranging from 101·39 to 107·38 cal./g. The last value, to which an uncertainty of ±0·07 is ascribed (Mathews, *J. Amer. Chem. Soc.*, 1926, **48**, 452), is however probably in error as the following argument shows. Since the virial coefficients have not been measured, corrections of the calculated latent heats of vaporization for gas imperfections can be only approximate. If for pyridine the value 0·8826 for d_4^{115} (Schiff, *Ber.*, 1886, **19**, 560) is taken, the value for V_L is 0·090 l./mole, and if the second virial coefficient of pyridine at its b. p. is assumed to equal that of benzene at its b. p. (*i.e.*, 970 cm.³/mole; see Francis, McGlashan, Hamann, and McManamey, *J. Chem. Phys.*, 1952, **20**, 1341), then the calorimetric latent heat should be 109·95 − 3·66, *i.e.*, 106·3 cal./mole. Since the second virial coefficient of pyridine is probably at least 970 cm.³/mole, it appears likely that the value 107·38 ± 0·07 cal./g. given by Mathews is too high. Since this sample was reported to have a b. p. of 114·13°, it was probably wet, and this would result in a high latent heat.

Calorimetric measurements of the latent heat of vaporization, in cal./g., for α-picoline (90·75, Kahlenberg, *J. Phys. Chem.*, 1901, **5**, 284; 92·7/127·73°, Constam and White, *Amer. Chem. J.*, 1903, **29**, 1) and for β-picoline (94·82/141·7°, *idem, ibid.*) have been reported and, as expected, the values are smaller than those in Table 3. Work on the determination of the virial coefficients of these bases is in progress.

Densities. Measurements of densities at 20° and at 30° were made by means of a Sprengel–Ostwald pycnometer (see Bauer, "Technique of Organic Chemistry," edited by Weissberger,

Interscience Publ., Inc., New York, 1949, Vol. I, p. 266). The capacity of the pycnometer was 13·5 ml. and the bores of the two limbs were 0·5 mm. and 0·2 mm. Both limbs could be closed by ground glass caps. The pycnometer design was modified slightly in that a millimetre scale was engraved on the wide-bore limb, and above this a small bulb was incorporated to allow for expansion of the liquid during weighing.

Before introduction of a sample, the pycnometer was dried by passage of air which had been dried over anhydrous magnesium perchlorate and filtered through glass wool. Each sample of base was dried by a distillation technique (Coulson, Hales, and Herington, *J.*, 1951, 2125), and it was shown that its water content after this treatment was sufficiently low to affect its density by less than 0·00001 g./ml. The sample was forced into the pycnometer, by means of a pressure of dried air, from a small vessel which was connected to the pycnometer by a ground glass joint, which was not greased. A guard-tube [$Mg(ClO_4)_2$] was attached to both limbs of the pycnometer by means of a T-tube, and the pycnometer was placed in a thermostat water-bath. The precautions described for the exclusion of water were shown to be adequate by analysis after the experiments.

The temperature of the bath was controlled to 0·005° and standardized by means of a platinum resistance thermometer. The level of the liquid in the wide-bore limb of the pycnometer was adjusted to fall within the scale. It was necessary to place a small electric heater around the expansion bulb while the pycnometer was in the bath, to prevent condensation of sample within this bulb. Error due to evaporation of sample from the capped pycnometer while the vessel was in the balance case was avoided as follows. The position of the meniscus in the wide limb was observed at known time intervals over short periods before the removal of the pycnometer from the bath for weighing, and after return of the pycnometer to the bath. The position of the meniscus was plotted against time, and from this graph the volume the sample would occupy if it were at the bath temperature at the time of weighing was found. The usual precautions were taken in preparing the vessels for weighing, and all weights were corrected to a vacuum.

The pycnometer was calibrated at 20° and at 30° by the use of pure water (Barber, Handley, and Herington, *Brit. J. Appl. Physics*, 1954, **5**, 41). Tilton and Taylor's values for the density of water, 0·9982336 g./ml. at 20°, and 0·9956783 g./ml. at 30° (*J. Res. Nat. Bur. Stand.*, 1937, **18**, 205) were used. The performance of the pycnometer was checked by determinations of the densities of a sample of pure benzene (purity 99·99 ± 0·005 moles %), mean values found being 0·87907 ± 0·00005 g./ml. at 20°, and 0·86836 ± 0·00005 g./ml. at 30°, to be compared with 0·87903 g./ml. at 20° (Forziati, Glasgow, Willingham, and Rossini, *ibid.*, 1946, **36**, 129), and 0·86836 g./ml. at 30° (Scatchard, Wood, and Mochel, *J. Phys. Chem.*, 1939, **43**, 119).

TABLE 4. *Observed densities at* 20° *and* 30° *of pyridine*, α-, β-, *and* γ-*picoline, and* 2 : 6-*lutidine, and calculated densities and coefficients of cubical expansion at* 25°.

$[d_{25} = 0{\cdot}5(d_{20} + d_{30})$; $\alpha_{25} = 0{\cdot}2(d_{20} - d_{30})/(d_{20} + d_{30})]$

Compound	d_{20} (g./ml.)	d_{30} (g./ml.)	d_{25} (g./ml.)	α_{25}
Pyridine	0·98310 ± 0·00000	0·97301 ± 0·00000	0·97806	0·001032 ± 0·000000
α-Picoline	0·94432 ± 0·00000	0·93503 ± 0·00002	0·93968	0·000989 ± 0·000002
β-Picoline	0·95658 ± 0·00000	0·94736 ± 0·00002	0·95197	0·000969 ± 0·000002
γ-Picoline	0·95478 ± 0·00000	0·94561 ± 0·00000	0·95020	0·000965 ± 0·000000
2 : 6-Lutidine ...	0·92257 ± 0·00002	0·91355 ± 0·00002	0·91806	0·000983 ± 0·000003

The observed densities of the five bases at 20° and at 30° (d_{20} and d_{30}) are given together with the standard deviations in Table 4. The values at 25° (d_{25}) were obtained by linear interpolation, and the coefficients of expansion at 25°, $\alpha_{25} = (1/V)(dV/dt)$, where V is the specific volume, were calculated by means of the equation $\alpha_{25} = 0{\cdot}2\ (d_{20} - d_{30})/(d_{20} + d_{30})$.

Eighty-five published density values for pyridine, 25 for α-picoline, 14 for β-picoline, 8 for γ-picoline, and 12 for 2 : 6-lutidine, for the temperature range 20—30° were collated. Our values for pyridine at 20° and at 30° (Table 4) are somewhat higher than those selected by Timmermans (*op. cit.*), but our value at 25° (Table 4) is identical with his. In the case of α-picoline, our value for 30° (Table 4) is 0·00012 g./ml. higher than that selected by Timmermans (*op. cit.*), but the values for 20° are identical.

The coefficient of cubical expansion now found for pyridine (Table 4) equals that (0·001) reported by Dutoit and Duperthuis (*J. Chim. phys.*, 1908, **6**, 699) within the accuracy of their work, but is considerably smaller than that (0·00114) recorded by Wright (*J.*, 1940, 870) for

the temperature range 25—78°. The data of Freiser and Glowacki (*loc. cit.*) lead to a value 0·00100 for the coefficient of cubical expansion of α-picoline for 20—30°.

Refractive indices. The critical-angle refractometer used (Bellingham and Stanley, London), embodied a 60° prism of refractive index 1·756269 (at 20°) for the D_1 line. Measurements were made at 0·6563, 0·5896, 0·5461, and 0·4861 μ. The scale of the instrument was calibrated and the refractive indices of the prism were determined by the National Physical Laboratory, Teddington, who also computed tables relating scale readings to refractive indices.

The refractive indices of these bases proved to be difficult to measure because not only are the bases hygroscopic but they are good solvents for greases. To exclude atmospheric moisture and avoid the presence of grease the apparatus shown in Fig. 1 was used in place of the corresponding parts supplied with the refractometer. The cell *A*, made of Pyrex glass, was thickened at the base and ground to fit the prism *F*. Care was taken in the thickening process to keep the glass as optically clear as possible, and an optical flat was ground on the outside at the point,

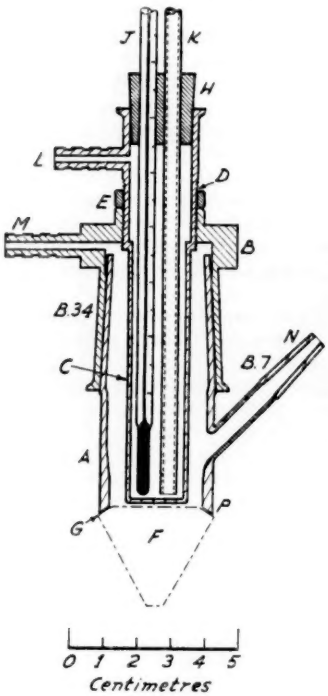


FIG. 1.

A. Pyrex glass cell.
B. Duralumin cover.
C. Duralumin well.
D. Screw thread.
E. Duralumin locking ring, with grub screw.
F. Prism.
G. Amalgamated lead washer.
H. Rubber bung.
J. Thermometer.
K. Inlet for water from thermostat.
L. Outlet for water.
M. Inlet for dry air.
N. Outlet for air, and sample inlet.
P. Window for incident light rays.

P, of entry of light rays from the monochromatic source. The cell was attached to the prism by means of an amalgamated lead washer *G*. The side-arm *N* carried a guard-tube [$Mg(ClO_4)_2$]. Before introduction of sample at *N*, the assembled cell was flushed out with dry air [$Mg(ClO_4)_2$]. Since the correct alignment of the prism could not be checked by observing the reflection of the telescope graticule from the top face of the prism when the cell was attached, a small auxiliary plane mirror fastened to the underside of the prism, parallel to the top face, was used to adjust the prism.

Measurements were made at 20·00° ± 0·01°, in a constant-temperature room (18—20°) with water from a thermostat circulated through the well, *C*, the prism jacket, and rubber tubing surrounding *A*. *B* and the upper part of *C* were lagged with cork. To prevent ingress of atmospheric moisture through the joints, which were not greased, a slight positive pressure of dry air was maintained within the cell.

Since it proved to be impossible to maintain and manipulate completely dry samples, measurements were made on specimens of varying water content and the results for the anhydrous compounds were obtained by graphical extrapolation. When necessary water was removed

from samples by simple distillation. The water content of a sample was determined immediately after the measurement of refractive index, by infra-red spectroscopy (Coulson, Hales, and Herington, *J.*, 1951, 2125).

FIG. 2. *Pyridine.*

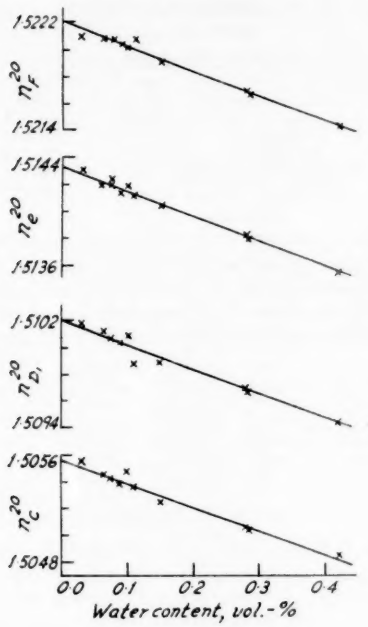


FIG. 3. *α-Picoline.*

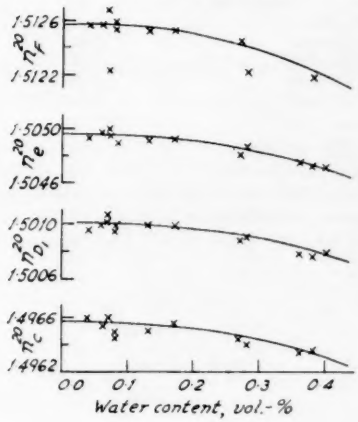


FIG. 4. *β-Picoline.*

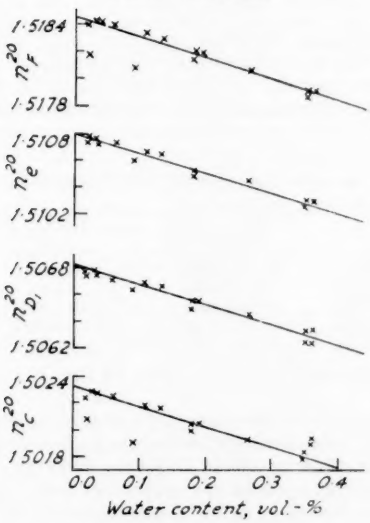
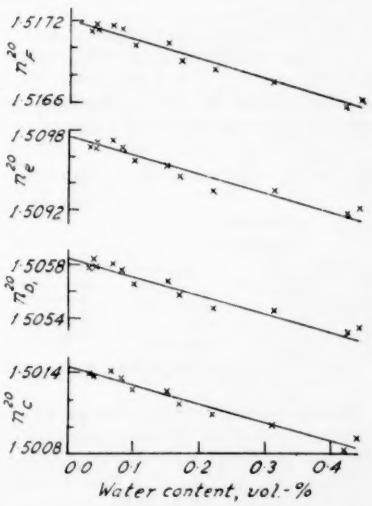


FIG. 5. *γ-Picoline.*



In Figs. 2—6 the refractive indices of the bases are plotted against water content (% by vol.). A small amount of water decreases the apparent refractive indices of pyridine and β- and γ-picoline, but is without effect on that of α-picoline. It increases that of 2 : 6-lutidine up

to a concentration of at least 1% of water. Refractive index is frequently used as a criterion of purity, but the present measurements show that it gives no certain indication of the water content of α-picoline or 2 : 6-lutidine.

Extrapolation of the data in Figs. 2—6 to zero water content gave the values shown in Table 5. The standard deviation of these values is believed to be of the order of ±0·00005 unit. The molar refractivities, $[R]^{20}_{D_1}$, for the D_1 line at 20° are also shown in Table 5.

TABLE 5. *Refractive indices and molar refractivities of anhydrous bases.*

Compound	n_C^{20}	$n_{D_1}^{20}$	n_e^{20}	n_F^{20}	$[R]^{20}_{D_1}$
Pyridine	1·50556	1·51020	1·51433	1·52221	24·071
α-Picoline	1·49657	1·50101	1·50496	1·5125	29·054
β-Picoline	1·50232	1·50682	1·51080	1·51845	28·963
γ-Picoline	1·50144	1·50584	1·50975	1·51720	28·970
2 : 6-Lutidine	1·49334	1·49767	1·50153	1·50895	34·025

The usefulness of the four-constant equation $n_\lambda = n_\infty + C/(\lambda - \lambda^*)^{1\cdot6}$ for the interpolation of precise refractive-index data for hydrocarbons has been shown by Forziati (*J. Res. Nat. Bur. Stand.*, 1950, **44**, 373), and the present experimental values for the C, D_1, and e lines (Table 5) have been fitted to an equation of this type. The data for these three lines were chosen rather than any involving the F line, because the experimental error of measurement was believed

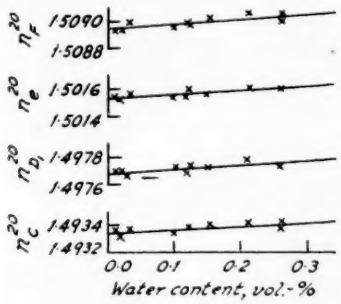


FIG. 6. 2 : 6-*Lutidine.*

to be greatest in the case of the F line. The technique of curve-fitting described by Forziati (*loc. cit.*) was employed, after the construction of suitable tables for the wave-lengths involved. The constants n_∞, C, and λ^* so obtained are listed in Table 6. By using these constants the refractive indices for the F line were calculated, and the differences between these and the observed values are shown in Table 6.

TABLE 6. *Values of the constants of Tilton and Gurewitz's modification of Hartmann's equation † for five pyridine bases.*

Compound	n_∞	C	λ^*	$(n_F^{20})_{calc.} - (n_F^{20})_{obs.}$
Pyridine	1·48675	0·006567	0·13824	+0·00011
α-Picoline	1·47854	0·006309	0·13750	+0·0001
β-Picoline	1·48367	0·006704	0·12864	−0·00002
γ-Picoline	1·48350	0·006309	0·13582	+0·00009
2 : 6-Lutidine	1·47588	0·006054	0·14050	+0·00006

† Tilton and Gurewitz, quoted by Forziati, *J. Res. Nat. Bur. Stand.*, 1950, **44**, 373.

Twelve refractive-index values for pyridine at 20°, 7 for α-picoline, 4 for β-picoline, 5 for γ-picoline, and 3 for 2 : 6-lutidine were collated. Our value for pyridine for the D_1 line agrees with that of Rozhdestvenskiĭ *et al.* [*Trans. Inst. Pure Chem. Reagents, U.S.S.R.*, 1935, **14**, 58] for the D_1–D_2 doublet (" *D* line ") but is significantly higher than the only other value, also referring to the D_1–D_2 doublet, listed in Timmermans's book (*op. cit.*). Theoretically, for these bases, the refractive indices for the D_1 line are 0·00002 unit lower than those for the D_1–D_2 doublet. In the case of α-picoline the new value for the D_1 line is only 0·00004 unit lower than that found by Freiser and Glowacki for the D_1–D_2 doublet (*loc. cit.*), and the new value

for the *e* line is only 0·00003 unit higher than that found by these workers (*loc. cit.*). If, however, the refractive index of α-picoline for the wave-length 0·4358 μ is calculated by means of the constants n_∞, C, and λ^* derived from the present measurements (see Table 6), the value 1·52224 is obtained. This is 0·00054 unit greater than that recorded by Freiser and Glowacki (*loc. cit.*). Thus it is very probable that their value for this wave-length is too low.

Infra-red absorption spectra. Coblentz ("Investigations of Infra-red Spectra," Carnegie Institute of Washington, 1905) described the spectra of liquid pyridine and α-picoline in the range 1—15 μ. Since then, spectra of other pyridine bases have been published, but with one exception the measurements were made on specimens of doubtful origin and purity. The exception is Freiser and Glowacki's work on α-picoline (*J. Amer. Chem. Soc.*, 1948, **70**, 2575; see also *Amer. Petroleum Inst.*, Research Project 44, spectrum Serial No. 743).

TABLE 7. *List of frequencies (cm.$^{-1}$) and rough estimates of intensities of the main absorption peaks for liquid samples.*

Pyridine		α-Picoline		β-Picoline		γ-Picoline		2 : 6-Lutidine	
702 vs	1690 w	729 s	1590 vs	708 vs	1659 w	728 s	1755 w	716 m	1471 vs
749 vs	~1745 w	751 vs	1776 w	788 vs	~1720 w	799 vs	1854 w	729 m	1584 vs
810 w	1827 w	798 m	1876 w	923 w	1838 w	872 w	1935 w	775 vs	1775 w
885 w	1876 w	883 w	1914 w	987 m	~1910 w	972 m	2025 w	889 w	~1873 w
~944 w	1926 m	972 m	1952 w	1028 s	1969 w	994 s	2200 w	972 m	1966 w
991 s	1992 w	994 s	2200 w	1106 s	2250 w	1042 s	2220 w	997 s	2230 w
1031 s	2210 w	1047 s	2380 w	1125 s	2375 w	1070 m	2310 w	1030 s	2340 w
1069 s	2300 w	1099 m	2450 w	1188 s	2465 w	1223 s	2440 w	1096 s	2450 w
1146 s	2440 w	1143 s	2600 w	1227 m	2600 w	1383 s	2740 w	1157 s	2635 w
1218 s	2590 w	1233 m	2720 w	1340 w	2755 w	1417 vs	2970 s	1224 s	2735 w
1293 w	2830 w	1291 s	2950 vs	1385 s	2895 s	~1445 s	3010 s	1248 s	2930 vs
1378 w	3030 s	1376 s	3030 vs	1414 vs	2980 s	1498 s	4120 w	1266 s	3060 vs
1439 vs	3080 s	~1440 vs	4080 w	1452 s	4065 w	1566 s	4260 w	1280 m	4060 w
1485 s	3650 w	1475 vs	4300 w	1479 vs	4315 w	1604 vs	4580 w	1374 s	4330 w
1584 vs	4070 w			1578 s	4590 w	1669 w		1456 vs	
1636 m	4600 w								

Spectrograms of our highly purified base samples were obtained with the double-beam infra-red spectrometer (Hilger D.209) described by Hales (*J. Sci. Instr.*, 1949, **26**, 359). These are very convenient for establishing rapidly the purity of samples consisting essentially of one base, while the use of certain of the absorption bands for the analysis of base mixtures has already been described (Coulson and Hales, *Analyst*, 1953, **78**, 114). Copies of the spectra of liquid and gaseous samples may be obtained on application to the Director, Chemical Research Laboratory. Lists of frequencies and rough estimates of intensities of the stronger absorption bands of liquid specimens are presented in Table 7 (s = strong, m = medium, w = weak, v = very).

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Studies in the Hydrolysis and Alcoholysis of Some Organic Nitrites.

By A. D. Allen.

[Reprint Order No. 5025.]

The kinetics and mechanisms of the hydrolysis of some simple organic nitrites were investigated, and the products of alcoholysis determined in some cases. The acid-catalysed hydrolysis of *n*-propyl, *tert.*-butyl, and diphenylmethyl nitrites has been studied at 0° in 72·5% (w/w) dioxan–water. In very dilute acid solution containing halide ions, the overall equation $-d[RO{\cdot}NO]/dt = k_2[H^+][RO{\cdot}NO] + k_3[H^+][RO{\cdot}NO][Halide^-]$ holds. The position of equilibrium between alkyl nitrite, water, nitrous acid, and the alcohol has been determined for *n*-propyl and *tert.*-butyl nitrites. A volumetric method for the determination of the total hydrolysable nitrous acid content of these esters is described. The alkaline hydrolysis of *n*-propyl and *tert.*-butyl nitrites has been studied in aqueous dioxan between 25° and 55°. The reactions are of the second order, but with *n*-propyl nitrite a small solvolytic component is indicated. Arrhenius parameters are given.

Except in the alcoholysis of triphenylmethyl nitrite, which leads to formation of the ether, nitrosyl–oxygen bond fission was found in all cases as is shown by retention of configuration during hydrolysis of optically-active 1-methylheptyl nitrite, by the alcoholysis products of *n*-propyl and *tert.*-butyl nitrites, and, for the *tert.*-butyl ester in acid solution, by the absence of olefin formation and by experiments with isotopically enriched water.

The results are interpreted in terms of the probable reaction mechanisms.

The investigations carried out here into the mechanisms of reactions of organic esters (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; Day and Ingold, *ibid.*, p. 686) have been extended to some simple organic nitrites. Fischer (*Z. physikal. Chem.*, 1908, **65**, 61) considered that the acid-catalysed hydrolysis of ethyl nitrite was too rapid at room temperature to be measured by conventional methods. Skrabal, Zahorka, and Wiemann (*ibid.*, 1939, *A*, **183**, 345) found that the rate of hydrolysis in slightly acid solutions containing acetate buffers increased slightly with methylation of the α-carbon atom in the series methyl—*tert.*-butyl nitrite. In alkaline solution the rates of hydrolysis were very much slower, but consistent results could not be obtained.

Acid Catalysis.—(i) n-*Propyl nitrite.* The hydrolysis of *n*-propyl nitrite has been studied at 0° in 72·5% (w/w) dioxan–water in the presence of small concentrations of mineral acids and their salts. The overall reaction is

$$Pr^nO{\cdot}NO + H_2O \overset{H^+}{\rightleftharpoons} Pr^n{\cdot}OH + HO{\cdot}NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

The position of equilibrium for this reaction was determined at 0° in various dioxan–water mixtures. Values for the concentration equilibrium constant $K = [ROH][HO{\cdot}NO]/[RO{\cdot}NO][HOH]$ were obtained for a wide range of initial concentrations giving a mean value of $K = 15{\cdot}7 \times 10^{-3}$. Individual results varied from 11·3 to $18{\cdot}6 \times 10^{-3}$.

With perchloric acid (0·001—0·007M) the observed first-order rate coefficients were found to be proportional to the hydrogen-ion concentration, the rate expression being :

$$-d[RO{\cdot}NO]/dt = k_1[RO{\cdot}NO] = k_2[H^+][RO{\cdot}NO] \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

First-order kinetics are observed in any one run, since the hydrogen-ion concentration is virtually unaffected by the weakly ionised nitrous acid released on hydrolysis. Since water is in large excess, its active mass is also constant, and is incorporated in k_1 and k_2.

In the presence of hydrochloric acid a faster rate of hydrolysis was observed than with

equivalent concentrations of perchloric acid. The rate was no longer directly proportional to the acid concentration, but could be expressed by the equation:

$$-d[RO{\cdot}NO]/dt = k_2[HCl][RO{\cdot}NO] + k_3[HCl]^2[RO{\cdot}NO] \quad . \quad . \quad . \quad . \quad . \quad (C)$$

Since hydrochloric acid is a strong acid under these conditions, the hydrogen-ion and chloride-ion concentrations may be equated to that of the acid added, and equation (*C*) may be written:

$$-d[RO{\cdot}NO]/dt = k_2[H^+][RO{\cdot}NO] + k_3[H^+][Cl^-][RO{\cdot}NO] \quad . \quad . \quad . \quad . \quad . \quad (D)$$

Table 1 shows the first-order rate constants for this ester at varying concentrations of the two acids. The results with perchloric acid give, for hydrogen-ion catalysis, a mean value of $k_2 = 0{\cdot}219$ sec.$^{-1}$ mole^{-1} l. This value is used in the interpretation of the results with hydrochloric acid, which give, for chloride-ion catalysis, a value of $k_3 = 39$ sec.$^{-1}$ mole^{-2} l.^{2}.

TABLE 1. n-*Propyl nitrite; acid catalysis.*

Temp. 0°. Solvent 72·5% dioxan–water.

$10^3[HClO_4]$, M	6·60	4·80	3·40	2·25	1·70	1·02	
10^4k_1, sec.$^{-1}$	14·3	10·4	7·55	4·94	3·70	2·26	
k_2, sec.$^{-1}$ mole^{-1} l.	0·217	0·217	0·222	0·220	0·218	0·222	
$10^3[HCl]$, M	3·90	3·40	3·00	2·62	1·90	1·42	0·70
10^4k_1, sec.$^{-1}$	13·9	11·35	9·95	8·35	5·75	4·18	1·84
k_3, sec.$^{-1}$ mole^{-2} l.^{2}	34·2	33·8	37·0	37·0	43·1	44·6	42·2

Consistently, the addition of sodium bromide to solutions of fixed hydrogen-ion (perchloric acid) concentration, and sufficient sodium perchlorate to maintain constant ionic strength, produced an increase in rate proportional to the concentration of added halide ions. This is in accordance with equation (*D*) when the first term is constant and only the halide ion varies in the second term. The results obtained were as follows:

n-*Propyl nitrite; bromide-ion catalysis.*

Temp. 0°. Solvent 72·5% dioxan–water. $[HClO_4] = 0{\cdot}0024$M.

$10^3[NaBr]$, M	11·6	10·2	6·60	4·40	2·40	0
10^4k_1, sec.$^{-1}$	13·0	12·3	9·64	8·52	7·02	5·49
k_3, sec.$^{-1}$ mole^{-2} l.^{2}	26·9	27·7	26·2	28·5	26·5	—

(ii) tert.-*Butyl nitrite.* The same conditions were used for the investigation of the acid-catalysed hydrolysis of this ester. Catalysis by hydrogen ions (perchloric acid) was found to be some 2—3 times greater, whilst catalysis by bromide ions was much less marked than with *n*-propyl nitrite. In both cases the catalysis was proportional to the concentrations of the respective ions. With this ester a small increase in rate was observed on addition of sodium perchlorate. Equilibrium determinations indicated that the hydrolysis is virtually complete under the conditions used for the kinetic studies. Table 2 shows the results obtained.

TABLE 2. tert.-*Butyl nitrites; acid catalysis.*

(a) *Perchloric acid.*

$10^3[HClO_4]$, M	3·70	2·96	2·34	2·22	1·78	1·48	1·21	0·74
10^4k_1, sec.$^{-1}$	19·4	15·5	12·0	11·3	9·02	7·55	6·04	3·67
k_2, sec.$^{-1}$ mole^{-1} l.	0·524	0·523	0·513	0·510	0·507	0·511	0·500	0·496

(b) *Sodium bromide.* $[HClO_4] = 0{\cdot}00234$M.

$10^3[NaBr]$, M	11·7	9·30	6·80	5·00	2·50	0
10^4k_1, sec.$^{-1}$	16·1	15·9	15·2	14·7	14·3	13·8
k_3, sec.$^{-1}$ mole^{-2} l.^{2}	8·4	9·6	8·8	7·7	8·5	—

(iii) *Diphenylmethyl nitrite.* A limited investigation was carried out on a small quantity of diphenylmethyl nitrite, to determine the order of magnitude of the catalytic constants. For hydrogen-ion catalysis, $k_2 = 0{\cdot}19$ sec.$^{-1}$ mole^{-1} l. and for bromide ions,

$k_3 = 27$ sec.$^{-1}$ mole^{-2} l.^{2}. These values are only approximate, since it was not practicable to purify the ester completely.

(iv) *Position of bond fission.* (−)-1-Methylheptyl nitrite was prepared by the action of nitrosyl chloride on (−)-octan-2-ol in pyridine. Since it is difficult to formulate a mechanism which would disturb the asymmetric centre, it is assumed that the configuration is retained, and thus the optical rotations of the two compounds with the same configuration are obtained. The optical course of the hydrolysis of this ester in acidic aqueous dioxan corresponded to complete retention of configuration. This implies fission of the nitrosyl–oxygen bond RO:---NO. The reverse reaction, between nitrous acid and (+)-octan-2-ol in water at 0°, produced (+)-1-methylheptyl nitrite in good yield without racemisation, showing that the reaction proceeds by nitrosation of the oxygen atom of the alcohol.

Bond-fission experiments with *tert.*-butyl nitrite were carried out by two methods. First an attempt was made to detect any small amounts of olefin which would inevitably be formed if any part of the acid-catalysed hydrolysis proceeded by a unimolecular alkyl–oxygen fission mechanism. No olefin could be detected by methods sensitive to as little as 0·1% of this product. The acid-catalysed hydrolysis was next carried out in the presence of water enriched with $H_2{}^{18}O$, supplied by Dr. D. R. Llewellyn of this Department. Any uni- or bi-molecular alkyl–oxygen fission would yield *tert.*-butanol containing an increased proportion of ^{18}O. The alcohol was separated by azeotropic distillation with benzene, and the isotopic composition of the water formed on pyrolysis was determined by Dr. C. A. Bunton, using the mass spectrometer. The ^{18}O content was normal. These two experiments show clearly that the hydrolysis of *tert.*-butyl nitrite under the conditions used proceeds exclusively by nitrosyl–oxygen fission, from which it is concluded that alkyl–oxygen fission is extremely unlikely in the hydrolysis of any simple alkyl nitrite under similar conditions.

The Mechanism of Acid-catalysed Hydrolysis.—The following mechanistic interpretations are consistent with our observations:

(1) $RO{\cdot}NO + H^+$	$\rightleftharpoons (RO{\cdot}NOH)^+$	Fast proton transfer
(2*a*) $(RO{\cdot}NOH)^+$	$\rightleftharpoons ROH + NO^+$	Unimolecular heterolysis
(2*b*) $(RO{\cdot}NOH)^+ + HOH$	$\rightleftharpoons ROH + (HO{\cdot}NOH)^+$	Bimolecular solvolysis
(2*c*) $(RO{\cdot}NOH)^+ + X^-$	$\rightleftharpoons ROH + NOX$	Bimolecular attack by halide ion
(3*a*) $NO^+ + HOH$	$\rightleftharpoons (HO{\cdot}NOH)^+$	Removal of products
(3*c*) $NOX + HOH$	$\rightleftharpoons HO{\cdot}NO + H^+ + X^-$	Removal of products
(4) $(HO{\cdot}NOH)^+$	$\rightleftharpoons HO{\cdot}NO + H^+$	Fast proton transfer

It is considered that the equilibria (1) and (4) are established rapidly, and are maintained throughout the reaction. Since the forward velocities of the rate-determining steps (2*a*), (2*b*), and (2*c*) are proportional to the concentration of the protonated ester, the position of equilibrium (1) for the different esters is probably a major factor in the observed variations in the rates of hydrolysis. It is also possible that the rapidity of the acid-catalysed hydrolysis of these esters, as compared with the much slower reactions of the simple carboxylic esters, may also be due largely to differences in the equilibrium concentrations of the protonated species.

There are three possible rate-determining steps. From the present results no definite distinction may be drawn between steps (2*a*) and (2*b*), since the kinetic forms of both are the same in aqueous solvents. However, the sensitivity of the reaction to small concentrations of halide ions indicates that attack by nucleophilic reagents takes place readily, and it therefore seems that the more probable mechanism involves the bimolecular attack by a water molecule, as in (2*b*). When halide ions are present in aqueous solution, the reactions (2*b*) and (2*c*) occur simultaneously, giving rise to the observed rate equation (*D*). The catalysis by halide ions, resulting in the intermediate formation of the nitrosyl halide, is analogous to the halide-ion catalysis of the rate of diazotisation of amines with acidified nitrous acid solutions (Schmid, *Z. Elektrochem.*, 1936, **42**, 579). The high reactivity of the protonated esters towards relatively weak nucelophilic reagents (water, halide ions), in contrast to the slow reaction of the esters, even with the strongly nucleophilic hydroxide ion, is also paralleled by the very great difference between the nitrosating power of the nitrous acidium ion $(HO{\cdot}NOH)^+$ and nitrous acid. Whereas the diazotisation of *o*-chloro-

aniline by the nitrous acidium ion proceeds rapidly in dilute solutions at 0°, the reaction with nitrous acid under similar conditions is undetectable (Ingold, *Bull. Soc. chim.* 1952, 667).

Alkaline Hydrolysis.—The hydrolysis of *n*-propyl and *tert.*-butyl nitrites has been studied in aqueous dioxan solutions in the presence of varying dilute concentrations of sodium hydroxide. The rate of disappearance of alkali was measured over the temperature range 25—55°. Under comparable conditions at 35° *tert.*-butyl nitrite is hydrolysed some 50 times more slowly than *n*-propyl nitrite, and owing to thermal decomposition of the former ester only the early stages of the hydrolysis could be followed accurately. Good second-order kinetics were observed in all cases, and the rate coefficients were in accordance with the relation: $\log_{10} k = \log_{10} A - E/(2{\cdot}303RT)$). Table 3 shows the results, together with the values of $\log_{10} A$ and E calculated from the Arrhenius equation.

TABLE 3. *Alkaline hydrolysis.*

Solvent, wt. % of dioxan	Ester	Initial [RO·NO], M	Initial [NaOH], M	10^6k_2, sec.$^{-1}$ mole^{-1} l. at 25·1°	35·1°	45·0°	55·1°	$\log_{10} A$	E, kcal.
72·5	Pr^n	0·025	0·054	26·5	81·6	185	465	9·17	18·7
60	,,	0·03	0·054	30·4	76·2	181	—	8·31	17·5
60	Bu^t	0·025	0·15	0·55	1·37	3·83	10·6	8·33	20·0
60	,,	0·12	0·15	0·43	1·27	3·71	—	9·22	21·3

With *n*-propyl nitrite the rate of hydrolysis over a wider range of initial concentrations of sodium hydroxide was investigated at 35° in 60% dioxan–water, and the following second-order rate coefficients were obtained:

Initial [NaOH,] M	0·055	0·114	0·115 (+0·117M-NaCl)	0·167
10^6k_2	75·5	67·8	64·0	58·1

Their decrease with increasing concentration of alkali may be attributed to an ionic strength effect, and/or to an underlying solvolytic reaction. The smaller decrease when sodium chloride is added shows that only a small part of the variation can be due solely to changing ionic strength. The instantaneous rate coefficients, $(1/[\text{RO·NO}])\, d[\text{RO·NO}]/dt = k_1 + k_2[\text{OH}^-]$, were plotted against hydroxide concentration. The slope of the straight line obtained gave a corrected value for $k_2 = 50{\cdot}5 \times 10^{-6}$ sec.$^{-1}$ mole^{-1} l., and the intercept gave $k_1 = 1{\cdot}5 \times 10^{-6}$ sec.$^{-1}$. Part of this value of k_1 is due to the ionic strength effect, and it should, therefore, be regarded as a maximum value for the solvolytic component of the reaction.

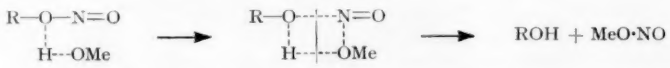
The position of bond fission under alkaline conditions was determined by following the optical course of the hydrolysis of (+)-1-methylheptyl nitrite in dilute alkaline aqueous ethyl alcohol. The configuration was retained, as found for the hydrolysis of 1-methylbutyl nitrite with concentrated alcoholic potash (Hoye, Ph.D. Thesis, London, 1953). It may, therefore, be concluded that the alkyl–oxygen bond of these esters remains intact during the reaction. Since the unimolecular heterolysis of the nitrosyl–oxygen bond is even less likely to occur in alkaline than in acid solution (Day and Ingold, *loc. cit.*, p. 702), it seems most probable that the alkaline hydrolysis proceeds by the nucleophilic attack of a hydroxide ion on the nitrogen atom of the ester.

Alcoholysis Reactions.—Kenyon and Young (*J.*, 1938, 965) have shown that the neutral alcoholysis of (−)-1-methylheptyl nitrite with *sec.*-butyl alcohol produces (−)-octan-2-ol. Since the occurrence of a small proportion of alkyl–oxygen fission might not have been detectable in this reaction, experiments were carried out in which *n*-propyl and *tert.*-butyl nitrites were separately dissolved in their respective alcohols, and sealed in dark glass containers at 35°. The formation of ethers by alkyl–oxygen bond fission is irreversible, so even a small amount of this mechanism would result in a gradual accumulation of the ether. On analysis after six weeks, no significant amount of the ether was detected in either mixture.

The occurrence of alkyl–oxygen fission was finally observed in the neutral alcoholysis of triphenylmethyl nitrite. The ester could not be isolated pure, owing to its very rapid

decomposition at room temperature, and the specimen used was a pasty yellow solid suspended in a small amount of dry ether. It reacted with dry methyl alcohol rapidly at room temperature, and the methyl nitrite formed was removed immediately by evaporation under reduced pressure: this procedure ensures that the products closely approximate to the true proportion of alkyl– to nitrosyl–oxygen bond fission. The methyl ether of triphenylmethyl alcohol was formed in good yield. Similar experiments with *n*-propyl alcohol gave the *n*-propyl ether as the sole product.

The comparative ease with which the simple alkyl nitrites react with methyl alcohol to give methyl nitrite must be reconciled with the very slow rate of hydrolysis in aqueous alkali. Neither a unimolecular process nor a simple nucleophilic attack by an alcohol molecule would be sufficiently rapid to account for the ester exchange reaction. A possible explanation may be that the initial step consists of the formation of a hydrogen bond between the solvent molecule and the ester, followed by a nucleophilic attack on the nitrogen atom :



The partial (or complete) transfer of a proton would increase the nucleophilic power of the alcohol molecule, and would also increase the susceptibility of the nitrogen atom to attack. The second stage would, therefore, be greatly facilitated. A comparative kinetic investigation with various nitrous esters would help to clarify this problem.

Experimental

Materials.—Dioxan was purified and dried by Vogel's method ("Practical Organic Chemistry," Longmans Green and Co., London, 1948, p. 175). *n*-Propyl and *tert.*-butyl nitrites were prepare in aqueous solution by Noyes's method (*Org. Synth.*, 1936, **16**, 7). They were distilled through a 12" helix-packed column under reduced pressure, and had b. p. 48·5°/760 mm., n_D^{20} 1·3605, n_D^{25} 1·3578 (Cowley and Partington, *J.*, 1933, 1252); and b. p. 63·5°/760 mm., n_D^{20} 1·3687, n_D^{25} 1·3660 (Coe and Doumani, *J. Amer. Chem. Soc.*, 1948, **70**, 1516). Octan-2-ol was resolved into its optical isomers by Kenyon's phthalic anhydride–brucine method (see Vogel, *op. cit.*, p. 489), giving (−)-octan-2-ol, b. p. 80°/15 mm., $[\alpha]_D^{18}$ −9·75°, and (+)-octan-2-ol, b. p. 80°/15 mm., $[\alpha]_D^{18}$ +9·41°. From the (+)-alcohol obtained, (+)-1-methylheptyl nitrite was prepared by the aqueous method of Noyes (*op. cit.*), giving b. p. 63—64°/15 mm., $[\alpha]_D^{18}$ +5·11°. (−)-1-Methylheptyl nitrite was prepared by the action of nitrosyl chloride on the (−)-alcohol in pyridine (Kenyon and Young, *loc. cit.*); it had b. p. 63—64°/15 mm., $[\alpha]_D^{18}$ −5·26°. Attempts to prepare diphenylmethyl nitrite and triphenylmethyl nitrite by this method failed: it was therefore modified by using exactly equimolecular quantities of the alcohol and pyridine in dry ether, and continuing the addition of nitrosyl chloride until a slight excess had been added. The pyridine hydrochloride was filtered off, and the ether removed by evaporation under reduced pressure. With diphenylmethyl nitrite a yellow liquid was obtained, which decomposed on distillation, even at 65°/0·1 mm. This product, which was used for the kinetic investigation, contained 81% of hydrolysable nitrous acid (Found: C, 75·4; H, 5·5%. This composition would be given approximately by a mixture of 80% diphenylmethyl nitrite and 20% diphenylmethyl alcohol). The triphenylmethyl nitrite so prepared was a pasty yellow solid which decomposed rapidly, becoming dark brown and evolving copious nitrous fumes, when the last traces of ether were removed. For the investigation of the products of alcoholysis, the crude preparation was used immediately without removing the last few ml. of ether.

Acid Hydrolysis.—Solutions were made up by weight from dioxan, carbon dioxide-free distilled water, and standard solutions of the acids and salts. The reaction flask was fitted with a jacketed automatic pipette, which was kept at the reaction temperature by circulating water from the ice–water thermostat. The appropriate ester (0·7—1 ml.) was added, and samples (7·80 ml.) of the solution were removed at intervals of 1—2 min., depending on the speed of the reaction, run into stoppered flasks containing carbon tetrachloride (35 ml.) and dilute sodium hydroxide (13 ml.; excess) at 0°, and titrated later with approximately 0·01N-

hydrochloric acid, 9 : 2 neutral red–bromothymol blue being used as mixed indicator. The following are details of two typical rate measurements in 72·5% dioxan–water at 0° :

(*a*) n-*Propyl nitrite* (perchloric acid = 0·0048N).

Time (min.)	0	2	3·5	5	6·5	8	9·5	11	12·5	∞
Titre (ml. HCl)	24·60	21·55	19·27	17·33	15·84	14·33	13·81	11·98	10·50	−1·80
$\log_{10}$ (titre–titre ∞) ...	1·422	1·368	1·324	1·282	1·247	1·208	1·165	1·139	1·090	—

The " infinity " titre is corrected to allow for the position of equilibrium under these conditions. The first-order rate coefficient, obtained from the graph of $\log_{10}$ (titre–titre ∞) against time, is $k_1 = 10{\cdot}4 \times 10^{-4}$ sec.$^{-1}$.

(*b*) tert.-*Butyl nitrite* (perchloric acid = 0·0023N).

Time (min.)	0	2	3	4	5	6	7	8	9	∞
Titre (ml. HCl)	28·59	25·55	23·94	22·64	21·42	20·26	19·21	18·16	17·17	4·94
$\log_{10}$ (titre–titre ∞) ...	1·373	1·314	1·279	1·248	1·217	1·185	1·154	1·121	1·087	—

The hydrolysis of this ester is complete (>99%) at equilibrium. These measurements give $k_1 = 12{\cdot}0 \times 10^{-4}$ sec.$^{-1}$.

Equilibrium Measurements.—Samples of the esters (0·4—1·7 g.) were weighed in small glass ampoules, which were crushed under dioxan–water solutions at 0° containing varying amounts of hydrochloric acid. In some cases the corresponding alcohol was also added. After about 20 half-lives of the hydrolysis samples were withdrawn and the free nitrous acid determined as described above. The total hydrolysable nitrous acid contained by the esters was determined by oxidation with ceric sulphate solution. Since the nitrous acid is removed the hydrolysis goes to completion, and the excess of ceric ion may be determined iodometrically. By this method, the samples of *n*-propyl nitrite used were found to contain 99% of the theoretical amount of nitrous acid, but the figure for *tert.*-butyl nitrite, even though freshly prepared, could not be increased above 96·8%.

Bond Fission.—(i) *Optical methods.* (−)-1-Methylheptyl nitrite, $[\alpha]_D^{18}$ −5·26° (2 ml.), was dissolved in dioxan (50 ml.) and water (5 ml.), and one drop of concentrated hydrochloric acid was added after the initial rotation had been measured; $[\alpha]_D^{18}$ −0·25° (*l*, 1) ⟶ −0·44° (3 days) ⟶ −0·46° (final, 5 days). The alkaline solution used contained sodium hydroxide (2 g.) in water (5 ml.) and ethanol (50 ml.). The (+)-1-methylheptyl nitrite, $[\alpha]_D^{18}$ +5·05° (4 ml.), was added, giving an initial rotation, α_D^{18} +0·40° (*l*, 1). During 7 days the rotation of the solution increased steadily, reaching a maximum of +0·68°.

(ii) *Olefin determinations.* The reaction mixture was dioxan–water (72·5%; 200 ml.), containing 0·01M-hydrochloric acid at 0°. The system was thoroughly swept out with nitrogen, and, with a slow stream of nitrogen passing continuously, *tert.*-butyl nitrite (5 ml.) was added. The exit gases passed through 20% sodium hydroxide solution, over solid potassium hydroxide, solid calcium chloride, and through *n*-heptane at −80°. After 20 min. the temperature of the reaction mixture was raised slowly to 45° and kept there for 30 min. to decompose all the nitrous acid. After the flask had cooled to 0° the heptane trap was removed and treated with bromine in carbon tetrachloride. The excess of bromine was titrated, potassium iodide and sodium thiosulphate being used [Found : Bromine remaining equivalent to (*a*) 25·35 ml., (*b*) 25·38 ml. of thiosulphate. Total bromine added = 25·37 ml. of thiosulphate].

(iii) *Acid hydrolysis with* $H_2{}^{18}O$. The reaction mixture was a mixture of dioxan (145 g.) and water (54 ml.) containing excess of ^{18}O. " AnalaR " 70% perchloric acid was added (0·2 ml.), and the mixture cooled to 0°. *tert.*-Butyl nitrite (10 ml.) was added, and after 20 min. the aqueous and the organic liquid were separated by the addition of dry sodium chloride (15 g.). The aqueous layer was extracted with dry ether, and the organic layer and ether washings together were neutralised and dried (K_2CO_3, followed by $CaSO_4$). Dry benzene (100 ml.) was added, and the mixture fractionated through a 36″ helix-packed electrically heated column. The *tert.*-butanol–benzene azeotrope (Young, *J.*, 1902, 746) was obtained, b. p. 73·1/760 mm., $n_D^{24\cdot8}$ 1·4490—1·4491 (C, 81·1; H, 10·35%). To check the identity of this product, a mixture of 60 g. of redistilled, dried " AnalaR " benzene and 40 g. of redistilled, lithium-dried *tert.*-butanol was fractionated. The azeotrope obtained had b. p. 73·1°/760 mm., $n_D^{24\cdot8}$ 1·4490 (Found : C, 81·5; H, 10·1%). Samples of the azeotrope from the hydrolysis were pyrolysed at 500° for 24 hr. : the products were condensed at −80°, and any volatile matter pumped off at that temperature. About 10 mm. of carbon dioxide was added and the tube resealed. After equilibrium had been established between the carbon dioxide and the water produced by the

pyrolysis (Cohn and Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 679) the ^{18}O content of the carbon dioxide was measured in the mass spectrometer by Dr. Bunton, and compared with samples of the same carbon dioxide which had been allowed to come to equilibrium with normal water. By using the formula: Total atom $\%^{18}O = 100/(2{\cdot}076R + 1)$, where R is the ratio of carbon dioxide of mass 44 : mass 46, the following results were obtained :

Source	Excess, atom %, of ^{18}O (over normal water) (1)	(2)
$H_2{}^{18}O$ water used	1·930	2·900
tert.-Butanol from hydrolysis	0·001	−0·002

Alkaline Hydrolysis.—Solutions were made up at room temperature from dioxan, carbon dioxide-free distilled water, " AnalaR " sodium hydroxide, and the appropriate ester. Equal samples (7·00 ml.) were sealed in hard-glass tubes and placed in thermostats. At appropriate times tubes were removed, cooled to 0°, crushed under carbon tetrachloride at 0°, and titrated as described earlier. " Infinity " values were found by crushing tubes under dioxan–water solutions containing a known excess of hydrochloric acid at 0°, and later titrating the total acid produced, making allowance for the position of equilibrium. Typical measurements, one for each ester, carried out at 35·1° in 60% (by weight) dioxan–water are given :

(*a*) n-*Propyl nitrite.*

Time (hr.)	0	17	24	40	51	68	94	164	185	∞
10^2[NaOH], M	5·44	4·81	4·60	4·26	4·06	3·82	3·50	3·05	2·97	2·52
10^6k_2 (sec.$^{-1}$ mole^{-1} l.)	—	78·5	83·5	76·5	72·5	75·0	78·0	78·0	78·0	—

(*b*) tert.-*Butyl nitrite.*

Time (hr.)	0	42	67	86	114	150	182	∞
10^2[NaOH], M	15·72	15·64	15·59	15·56	15·50	15·45	15·40	13·26
10^6k_2 (sec.$^{-1}$ mole^{-1} l.)	—	1·38	1·39	1·39	1·46	1·39	1·37	—

Alcoholyses.—*n*-Propyl nitrite (62 ml.) and dry *n*-propyl alcohol (120 ml.) were sealed in a dark-glass flask, and kept at 35° for 6 weeks. The ester was distilled off and the residue extracted with water and ether. The ether extract was dried and distilled, leaving a residue (3·5 ml.), b. p. >50°. This was extracted with water (20 ml.), and the remaining organic liquid (1·5 ml.) was distilled from sodium giving a liquid (1 ml.), b. p. 88°, n_D^{20} 1·3818 (cf. *n*-propyl alcohol, b. p. 97°, n_D^{20} 1·3833, and di-*n*-propyl ether, b. p. 90°, n_D^{20} 1·3809). *tert.*-Butyl nitrite (60 ml.) and dry *tert.*-butyl alcohol (120 ml.) were mixed and treated as above. About 0·5 ml. of residue was obtained, which reacted completely with sodium metal, giving a negligible distillate.

Dry methyl alcohol (50 ml.) was added to triphenylmethyl nitrite suspension in dry ether (6 ml.). The solution was evaporated rapidly under reduced pressure, while the temperature was raised to 35°. Successive crystalline fractions were obtained; the three major fractions (3·3 g.) had m. p. 82—83°, leaving a residue (0·3 g.), m. p. 100—120° (Found, for the second fraction : C, 88·2; H, 6·5. Calc. for methyl triphenylmethyl ether : C, 87·6; H, 6·6%). A control experiment with triphenylmethyl alcohol in dry methyl alcohol gave only triphenylmethyl alcohol, m. p. 161°. A second portion (6 ml.) of the ester in ether was added to dry *n*-propyl alcohol (50 ml.), and kept at room temperature for 48 hr. The solution was evaporated at reduced pressure, leaving 5 ml. of a yellow oil which was recrystallised with difficulty from methyl alcohol and water. Pale yellow crystals (3·9 g.) were obtained, m. p. 55° (Found : C, 87·1; H, 7·3. Calc. for *n*-propyl triphenylmethyl ether : C, 87·3; H, 7·3%).

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Thiophen Derivatives of Biological Interest. Part VI. The Chemistry of* 2-tert.-*Butylthiophen.*

By Michel Sy, Ng. Ph. Buu-Hoï, and Ng. D. Xuong.

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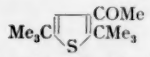
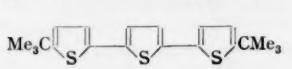
The preparation and properties of 2-*tert.*-butylthiophen have been investigated, and a large number of its derivatives (some with potential pharmacological interest) has been prepared and orientated. One product of the stannic chloride-catalysed alkylation of thiophen with *tert.*-butyl chloride is shown by direct synthesis to be 5 : 5′-di-*tert.*-butyl-2 : 2′-dithienyl, and another is probably 2 : 5-di-(5-*tert.*-butyl-2-thienyl)thiophen.

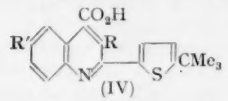
The *tert.*-butylation of thiophen was first investigated by Kutz and Corson (*J. Amer. Chem. Soc.*, 1946, **68**, 1477) who used *iso*butylene or *tert.*-butyl alcohol as alkylating agent and montmorillonite clays as catalyst; the monoalkylated product thus obtained was later found to be a mixture of 2- and 3-*tert.*-butylthiophen (Appleby, Sartor, Lee, and Kapranos, *ibid.*, 1948, **70**, 1552). The use of *iso*butylene and 75% sulphuric acid has also been advocated (Caesar, *ibid.*, p. 3623); but a most convenient procedure has now been found in the use of *tert.*-butyl chloride and stannic chloride in carbon disulphide. Good yields were thus afforded of a monoalkyl product consisting of 75% of 2-*tert.*-butylthiophen and 25% of the 3-isomer; as earlier methods gave roughly equal quantities of the two isomers, the effect of the catalyst is obvious. This is further demonstrated by the fact that the dialkylated product isolated consisted almost entirely of 2 : 5-di-*tert.*-butylthiophen, also obtained from 2-*tert.*-butylthiophen and *tert.*-butyl chloride by the same method; it was characterised by its crystallised 3-acetyl derivative (I). By contrast, Caesar's method yielded a mixture of di-*tert.*-butylthiophens from which no pure constituent could be isolated, and which gave an impure ketone on acetylation. The 2 : 5-directing influence of stannic chloride is reminiscent of the *para*-orienting effect of ferric chloride in the *tert.*-butylation of toluene (Bialobrzeski, *Ber.*, 1897, **30**, 1773; Buu-Hoï and Cagniant, *Bull.*

(I) 

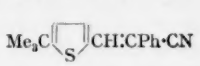
Soc. chim., 1942, **9**, 887; for similar cases, see Illingworth and Peters, *J.*, 1951, 1602), a reaction which led to considerable *meta*-alkylation when a stronger catalyst such as aluminium chloride or sulphuric acid was used (Baur, *Ber.*, 1891, **24**, 2833). Another interesting feature of the *tert.*-butylation by means of stannic chloride was the formation of substantial yields of two higher-boiling by-products, one of which was identified as 5 : 5′-di-*tert.*-butyl-2 : 2′-dithienyl (II) by an Ullmann synthesis from 2-*tert.*-butyl-5-iodothiophen, the other being probably 2 : 5-di-(5-*tert.*-butyl-2-thienyl)thiophen (III), on the grounds of composition,



(III)



(IV)



(V)

molecular weight, and physical properties. In these side-reactions, stannic chloride clearly acted as an oxidising agent. The easy formation of a terthienyl derivative is remarkable, in view of the difficulties generally encountered in the synthesis of such compounds.

2-*tert.*-Butylthiophen readily underwent stannic chloride-catalysed Friedel–Crafts acylations to give 5-acetyl, 5-propionyl, and 5-*n*-butyryl derivatives; the site of substitution was determined by sodium hypobromite oxidation of the first-named ketone to 5-*tert.*-butyl-2-thenoic acid (Messina and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 920); 2-*tert.*-butyl-5-methylthiophen, which these authors synthesised, was also obtained by a Kishner–Wolff–Huang-Minlon reduction of 5-*tert.*-butyl-2-thenaldehyde, prepared from 2-*tert.*-butylthiophen, *N*-methylformanilide, and phosphorus oxychloride (cf. King and

* Part V, Nam, Buu-Hoï, and Xuong, *J.*, 1954, 1690.

Nord, *J. Org. Chem.*, 1948, **13**, 635; Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130). 2-*tert.*-Butyl-5-ethyl-, -5-*n*-propyl-, and -5-*n*-butyl-thiophen were similarly prepared. Nitration of 2-*tert.*-butylthiophen afforded the 5-nitro-derivative, and that of 2-acetyl-5-*tert.*-butylthiophen gave 5-acetyl-2-*tert.*-butyl-3-nitrothiophen, both of which had a pleasant odour.

Several derivatives of 2-*tert.*-butylthiophen of potential pharmacodynamic interest were prepared for biological testing. The thiosemicarbazones of 5-*tert.*-butyl-2-thenaldehyde and 2-acetyl-5-*tert.*-butylthiophen had important tuberculostatic activity *in vitro* (cf. Welsch, Buu-Hoï, *et al.*, *Compt. rend.*, 1951, **232**, 1608); condensation with chloroacetic acid gave the corresponding 4-oxo-Δ^2-thiazolin-2-ylhydrazones of very slight activity (cf. Buu-Hoï, Hoán, and Lavit, *J.*, 1952, 4590). 5-*tert.*-Butyl-2-thenoyl chloride gave, with diethylaminoethanol, diethylaminoethyl 5-*tert.*-butyl-2-thenoate, whose hydrochloride showed local anæsthetic properties. The atophan-like 2-(5-*tert.*-butyl-2-thienyl)cinchoninic acid and its 3-methyl and 6-bromo-derivatives [cf. (IV)] were prepared by Pfitzinger reactions from 2-acyl-5-*tert.*-butylthiophens (cf. Buu-Hoï *et al.*, *J. Org. Chem.*, 1953, **18**, 1209).

Condensation of 5-*tert.*-butyl-2-thenaldehyde with benzyl cyanide in the presence of sodium hydroxide yielded β-(5-*tert.*-butyl-2-thienyl)-α-phenylacrylonitrile (V). Hydrogenolysis with Raney nickel of 5-*tert.*-butyl-2-thenoic acid (cf. Papa, Schwenk, and Ginsberg, *J. Org. Chem.*, 1949, **14**, 723; Blicke and Sheets, *J. Amer. Chem. Soc.*, 1948, **70**, 3768) readily gave ω-*tert.*-butyl-*n*-valeric (6 : 6-dimethylheptanoic) acid; the extension of this convenient method to the preparation of further ω-*tert.*-butyl fatty acids of biological interest will be reported later.

Experimental

tert.-*Butylation of Thiophen.*—To an ice-cooled, well-stirred solution of thiophen (168 g.) and *tert.*-butyl chloride (222 g.) in anhydrous carbon disulphide (3000 c.c.), contained in a flask fitted with a calcium chloride tube, stannic chloride (627 g.) was added dropwise (1 hr.). The orange-coloured mixture was kept for 5 hr. at room temperature, and poured into ice-cooled dilute hydrochloric acid. The organic layer was washed with dilute aqueous sodium hydroxide, then with water, and dried ($CaCl_2$). The residue from evaporation of the solvent gave on distillation an 85—88% yield of alkylated products (240 g.). The lower-boiling portions were fractionated by means of a 30-plate Vigreux column, to give 2-*tert.*-butylthiophen (120 g.), b. p. 165°, n_D^{23} 1·5024, 3-*tert.*-butylthiophen (40 g.), b. p. 172°, n_D^{23} 1·5020, and a 15—20% yield of di-*tert.*-butylthiophens (40—50 g.), which consisted mainly of 2 : 5-*di*-tert.-*butylthiophen*, b. p. 219°, n_D^{24} 1·4964 (Found : C, 73·2; H, 10·2. $C_{12}H_{20}S$ requires C, 73·5; H, 10·2%). The higher-boiling portions yielded on vacuum-fractionation : (*a*) 5 : 5′-*di*-(tert.-*butyl*-2 : 2′-*dithienyl*) (15—20 g.), b. p. 200—202°/13 mm., which crystallised as shiny, colourless needles, m. p. 89°, from methanol (Found : C, 68·9; H, 7·9. $C_{16}H_{22}S_2$ requires C, 69·1; H, 7·9%); (*b*) 2 : 5-*di*-(5-tert.-*butyl*-2-*thienyl*)*thiophen*, crystallising as yellow needles (15—20 g.), b. p. 275—285°/13 mm., m. p. 116°, from methanol (Found : C, 66·5; H, 6·6. $C_{20}H_{24}S_3$ requires C, 66·7; H, 6·7%).

Synthesis of 5 : 5′-*Di*-tert.-*butyl*-2 : 2′-*dithienyl* (II).—To an ice-cooled solution of 2-*tert.*-butylthiophen (12 g.) in dry benzene (15 c.c.), iodine (30 g.) and yellow mercuric oxide (20 g.) were alternately added (20 min.); the mixture was kept for 1 hr. at room temperature, then filtered, and the solid washed with ether (25 c.c.). The ether–benzene filtrate was washed with aqueous sodium hydrogen sulphite and dried ($CaCl_2$), and the solvents were removed. The residue gave on vacuum fractionation 2-tert.-*butyl*-5-*iodothiophen* (21 g.), as a yellow liquid, b. p. 123°/13 mm., n_D^{22} 1·5832, darkening on exposure to light (Found : C, 36·0; H, 4·0. $C_8H_{11}SI$ requires C, 36·1; H, 4·1%). A mixture of this compound (20 g.) with copper powder (15 g.) was cautiously refluxed at 190—200° for 30 min., and the product vacuum-fractionated, giving in 80% yield 5 : 5′-di-*tert.*-butyl-2 : 2′-dithienyl, b. p. 200°/13 mm., identical with the by-product from the *tert.*-butylation of thiophen.

5-tert.-*Butyl*-2-*thenaldehyde.*—A mixture of 2-*tert.*-butylthiophen (17·5 g.), *N*-methylformanilide (22·5 g.), and phosphorus oxychloride (24 g.) was refluxed for 2 hr., then cooled; an aqueous solution of sodium acetate was added, and the product worked up in the usual way, giving in 80% yield 5-tert.-*butyl*-2-*thenaldehyde*, as a pale yellow oil, b. p. 246°, n_D^{22} 1·5495 (Found : C, 64·2; H, 7·2. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%); it gave a *semicarbazone*, colourless leaflets, m. p. 249° (from methanol) (Found : C, 53·3; H, 6·5. $C_{10}H_{15}ON_3S$ requires C, 53·3; H, 6·7%), *thiosemicarbazone*, colourless needles, m. p. 197° (from ethanol) (Found : C, 49·5;

H, 6·3. $C_{10}H_{15}N_3S_2$ requires C, 49·8; H, 6·2%), a *4-oxo-Δ²-thiazolin-2-ylhydrazone*, colourless leaflets, m. p. 318° (from ethanol) (Found: C, 51·0; H, 5·2. $C_{12}H_{15}ON_3S_2$ requires C, 51·2; H, 5·3%), and an *oxime*, colourless prisms, m. p. 86° (from aqueous methanol) (Found: C, 59·0; H, 7·3. $C_9H_{13}ONS$ requires C, 59·0; H, 7·1%). A *tert.*-butyl-2-thenaldehyde of unknown constitution prepared by Hartough and Dickert (*J. Amer. Chem. Soc.*, 1949, **71**, 3922) was recorded as boiling at 155—162°/1 mm., and giving a semicarbazone, m. p. 212—214°; Messina and Brown (*loc. cit.*) obtained by a Sommelet reaction with *5-tert.*-butyl-2-thenoyl chloride an aldehyde whose semicarbazone had m. p. 215—216°.

2-tert.-*Butyl-5-methylthiophen*.—A solution of the foregoing aldehyde (8·5 g.) and 85% hydrazine hydrate (14 g.) in diethylene glycol (60 c.c.) was warmed for a few minutes, heated with potassium hydroxide (14 g.) with removal of water, then refluxed for 3 hr. After cooling, water was added, and the product taken up in benzene, washed with dilute hydrochloric acid, and purified by distillation. A 92% yield was obtained of a colourless oil, b. p. 183°, n_D^{23} 1·5031. Messina and Brown (*loc. cit.*), who prepared 2-*tert.*-butyl-5-methylthiophen from 6 : 6-dimethylheptane-2 : 5-dione and phosphorus pentasulphide, gave b. p. 74—75°/19 mm.

β-(5-tert.-*Butyl-2-thienyl*)-α-*phenylacrylonitrile* (V).—To a warm solution of equimolecular amounts of *5-tert.*-butyl-2-thenaldehyde and benzyl cyanide in ethanol, a few drops of 40% aqueous sodium hydroxide were added; the solid *nitrile* obtained on cooling formed pale yellow needles, m. p. 100°, from ethanol, giving an orange colour with sulphuric acid (Found: C, 76·3; H, 6·2. $C_{17}H_{17}NS$ requires C, 76·4; H, 6·4%).

2-*Acetyl*-5-tert.-*butylthiophen*.—To an ice-cooled solution of 2-*tert.*-butylthiophen (14 g.) and acetyl chloride (8 g.) in carbon disulphide (200 c.c.), stannic chloride was added dropwise with stirring; the mixture was kept for 1 hr. at room temperature, then poured on ice-cooled aqueous hydrochloric acid, the organic layer washed with a dilute solution of sodium hydroxide, then with water, the solvent removed, and the residue vacuum-distilled. The *ketone* (16 g., 88%) was a pale yellow oil, b. p. 255°, 146°/13 mm., n_D^{25} 1·5363 (Found: C, 65·8; H, 7·7. $C_{10}H_{14}OS$ requires C, 65·9; H, 7·7%), and gave a *semicarbazone*, colourless leaflets, m. p. 252° (Found: C, 55·1; H, 7·2. $C_{11}H_{17}ON_3S$ requires C, 55·2; H, 7·1%), a *thiosemicarbazone*, yellowish needles, m. p. 194° (Found: C, 51·5; H, 6·5. $C_{11}H_{17}N_3S_2$ requires C, 51·8; H, 6·7%), and a *4-oxo-Δ²-thiazolin-2-ylhydrazone*, colourless prisms, m. p. 315° (Found: C, 52·6; H, 5·7. $C_{13}H_{17}ON_3S_2$ requires C, 52·9; H, 5·8%), all from ethanol; the 2 : 4-*dinitrophenylhydrazone* formed shiny, orange-red needles, m. p. 222°, from acetic acid (Found: N, 15·2. $C_{16}H_{18}O_4N_4S$ requires N, 15·5%); the *oxime* crystallised as colourless prisms, m. p. 118°, from methanol (Found: C, 60·9; H, 7·5. $C_{10}H_{15}ONS$ requires C, 60·9; H, 7·6%). Hartough and Conley (*J. Amer. Chem. Soc.*, 1947, **69**, 3097) obtained from unfractionated *tert.*-butylthiophen an acetyl derivative, b. p. 114°/4 mm., n_D^{20} 1·5343, giving a semicarbazone, m. p. 209—210°.

5-*Acetyl*-2-tert.-*butyl*-3-*nitrothiophen*.—To an ice-cooled solution of nitric acid (8 g.; *d* 1·51) in acetic anhydride (30 c.c.), a solution of the foregoing ketone (18·2 g.) in acetic anhydride (30 c.c.) was added dropwise with stirring; the mixture was kept at room temperature for 2 hr., then poured on ice, and the precipitate washed thoroughly with cold water and recrystallised twice from ligroin; the *nitro-ketone* formed yellow leaflets, m. p. 80° (Found: C, 52·8; H, 5·8. $C_{10}H_{13}O_3NS$ requires C, 52·9; H, 5·7%).

2-tert.-*Butyl-5-nitrothiophen*.—Similarly prepared from 2-*tert.*-butylthiophen, this *nitro*-compound formed yellow leaflets, m. p. 74°, from ligroin (Found: C, 51·6; H, 6·2. $C_8H_{11}O_2NS$ requires C, 51·8; H, 5·9%); it could be reduced with tin and hydrochloric acid to the corresponding amine.

2-tert.-*Butyl-5-ethylthiophen*.—Prepared from 2-acetyl-5-*tert.*-butylthiophen and hydrazine hydrate in the usual way, this *thiophen* formed a colourless oil, b. p. 201°, n_D^{23} 1·5010 (Found: C, 71·4; H, 9·5. $C_{10}H_{16}S$ requires C, 71·4; H, 9·4%).

2-tert.-*Butyl-5-propionylthiophen*.—Prepared from 2-*tert.*-butylthiophen (14 g.), propionyl chloride (9·5 g.), and stannic chloride (30 g.) in carbon disulphide (200 c.c.), this *propionyl* compound formed a pale yellow oil (16 g.), b. p. 269°, 152°/13 mm., n_D^{22} 1·5313 (Found: C, 67·2; H, 8·2. $C_{11}H_{16}OS$ requires C, 67·3; H, 8·2%). The *semicarbazone* formed colourless leaflets, m. p. 235° (Found: C, 56·6; H, 7·7. $C_{12}H_{19}ON_3S$ requires C, 56·9; H, 7·5%), the *thiosemicarbazone*, yellowish needles, m. p. 187° (Found: C, 53·3; H, 7·0. $C_{12}H_{19}N_3S_2$ requires C, 53·5; H, 7·1%), and the *4-keto-Δ²-thiazolin-2-ylhydrazone*, colourless prisms, m. p. 309° (Found: C, 54·0; H, 6·2. $C_{14}H_{19}ON_3S_2$ requires C, 54·4; H, 6·1%), all from ethanol; the *oxime* formed colourless needles, m. p. 116° (Found: N, 6·5. $C_{11}H_{17}ONS$ requires N, 6·6%).

2-tert.-*Butyl*-5-n-*propylthiophen*, formed by reduction, was a colourless oil, b. p. 222°, n_D^{22} 1·4984 (Found: C, 72·4; H, 10·0. $C_{11}H_{18}S$ requires C, 72·5; H, 9·9%); a by-product was

the *azine* of 2-*tert.*-butyl-5-propionylthiophen, b. p. 255°/13 mm., crystallising from methanol as yellow needles, m. p. 121° (Found : N, 7·0. $C_{22}H_{32}N_2S_2$ requires N, 7·2%).

5-tert.-*Butyl*-2-n-*butyrylthiophen*.—This *ketone* (16 g.), prepared from 2-*tert.*-butylthiophen (14 g.), *n*-butyryl chloride (11 g.), and stannic chloride (30 g.) in carbon disulphide (200 c.c.), was a pale yellow oil, b. p. 159°/13 mm., n_D^{22} 1·5293 (Found : C, 68·5; H, 8·8. $C_{12}H_{18}OS$ requires C, 68·6; H, 8·6%); its *semicarbazone* formed colourless prisms, m. p. 205°, from ethanol (Found : C, 58·2; H, 8·0. $C_{13}H_{21}ON_3S$ requires C, 58·4; H, 7·9%).

2-n-*Butyl*-5-tert.-*butylthiophen* was obtained in the usual way from the foregoing ketone and hydrazine hydrate as a colourless oil, b. p. 116°/13 mm., n_D^{23} 1·4958 (Found : C, 73·5; H, 10·5. $C_{12}H_{20}S$ requires C, 73·5; H, 10·2%), together with a by-product, the *azine* of 5-*tert.*-butyl-2-*n*-butyrylthiophen, b. p. 278°/13 mm., crystallising as long yellow needles, m. p. 119°, from methanol (Found : N, 6·7. $C_{24}H_{36}N_2S_2$ requires N, 6·7%).

3-*Acetyl*-2 : 5-*di*-tert.-*butylthiophen* (I).—This *ketone* (12 g.), obtained from 2 : 5-di-*tert.*-butylthiophen (13 g.), acetyl chloride (6 g.), and stannic chloride (20 g.) in carbon disulphide (150 c.c.), had b. p. 162°/13 mm., and crystallised as colourless prisms, m. p. 78°, from ligroin (Found : C, 70·3; H, 9·4. $C_{14}H_{22}OS$ requires C, 70·6; H, 9·2%); it did not give a semicarbazone, and could not be oxidised to the corresponding acid by sodium hypobromite, or caused to undergo Pfitzinger reactions. Hartough and Conley (*loc. cit.*) obtained from a mixture of di-*tert.*-butylthiophens a ketone, b. p. 105°/3 mm., m. p. 54—55°.

Diethylaminoethyl 5-tert.-*Butyl*-2-*thenoate*.—5-*tert.*-Butyl-2-thenoic acid, prepared in 90% yield from 2-acetyl-5-*tert.*-butylthiophen (19·1 g.) and aqueous sodium hypobromite (from 16 g. of sodium hydroxide and 8·2 c.c. of bromine), formed colourless needles, m. p. 126°, from water; Schick and Hartough (*J. Amer. Chem. Soc.*, 1948, **70**, 1645) gave m. p. 128—128·5°. The corresponding *chloride*, prepared by means of thionyl chloride, was a pale yellow oil, b. p. 120—122°/13 mm., n_D^{23} 1·5522 (Found : C, 53·0; H, 5·3. $C_9H_{11}OSCl$ requires C, 53·3; H, 5·3%); the *amide* formed colourless prisms, m. p. 148°, from methanol (Found : C, 58·8; H, 7·3. $C_9H_{13}ONS$ requires C, 59·0; H, 7·1%). *Diethylaminoethyl* 5-tert.-*butyl*-2-*thenoate*, prepared from the foregoing acid chloride (10 g.) and diethylaminoethanol (14 g.) in benzene, was a thick, pale yellow oil, b. p. 198°/13 mm., n_D^{22} 1·5143 (Found : C, 63·3; H, 8·7. $C_{15}H_{25}O_2NS$ requires C, 63·6; H, 8·8%), which gave a hydrochloride, crystallising as hygroscopic, colourless prisms, m. p. 118°, from methanol.

2-(5-tert.-*Butyl*-2-*thienyl*)*cinchoninic Acid* (IV; R = R′ = H).—A solution of equimolecular amounts of 2-acetyl-5-*tert.*-butylthiophen and isatin in ethanol was refluxed with potassium hydroxide (3 mol.) for 24 hr.; water was added, the neutral impurities were removed by ether-extraction, and the precipitate obtained on acidification with acetic acid was recrystallised from ethanol; the *cinchoninic acid* formed yellowish prisms, m. p. 185° (Found : C, 69·1; H, 5·3. $C_{18}H_{17}O_2NS$ requires C, 69·5; H, 5·5%); 2-(5-tert.-*butyl*-2-*thienyl*)*quinoline*, obtained by heating this acid above its m. p. and vacuum-distillation of the residue, formed colourless prisms, m. p. 65°, from methanol (Found : N, 5·2. $C_{17}H_{17}NS$ requires N, 5·2%), giving a picrate crystallising as deep yellow needles, m. p. 202°, from ethanol.

6-*Bromo*-2-(5-tert.-*butyl*-2-*thienyl*)*cinchoninic acid* (IV; R = H, R′ = Br), prepared with 5-bromoisatin, formed yellow needles, m. p. 237° (decomp.), from ethanol (Found : C, 55·1; H, 4·3. $C_{18}H_{16}O_2NSBr$ requires C, 55·4; H, 4·1%).

2-(5-tert.-*Butyl*-2-*thienyl*)-3-*methylcinchoninic acid* (IV; R = Me, R′ = H), prepared from isatin and 2-*tert.*-butyl-5-propionylthiophen, formed yellowish prisms, m. p. 267° (decomp.) (Found : C, 70·0; H, 6·1. $C_{19}H_{19}O_2NS$ requires C, 70·1; H, 5·8%).

Hydrogenolysis of 5-tert.-*Butyl*-2-*thenoic Acid*.—To a well-stirred solution of this acid (12 g.) in 10% aqueous sodium hydroxide (100 c.c.) heated at 90°, Raney nickel (100 g.) was added in small portions with a few drops of *iso*amyl alcohol to prevent excessive frothing; the mixture was then heated for 2 hr. and filtered hot, and the cooled filtrate acidified with hydrochloric acid; the product was taken up in ether and purified by vacuum-distillation; 6 : 6-*dimethylheptanoic acid*, thus obtained in 70% yield, was a pale yellow oil with an unpleasant rancid smell, b. p. 143°/17 mm., n_D^{22} 1·4375 (Found : C, 68·3; H, 11·5. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%); the corresponding *chloride* was a pale yellow oil, b. p. 90°/13 mm., n_D^{22} 1·4522 (Found : C, 61·5; H, 9·9. $C_9H_{17}OCl$ requires C, 61·2; H, 9·6%); the *amide* formed colourless needles, m. p. 106°, from benzene (Found : N, 9·0. $C_9H_{19}ON$ requires N, 8·9%); and NN′-*bis*-(6 : 6-*dimethylheptanoyl*)-p-*phenylenediamine*, prepared from the acid chloride with *p*-phenylenediamine in pyridine (cf. Buu-Hoï, *Bull. Soc. chim.*, 1945, **12**, 587), formed colourless needles, m. p. 224°, from methanol (Found : N, 7·0. $C_{34}H_{40}O_2N_2$ requires N, 7·2%).

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The Molecular Rotations of Polycyclic Compounds. Part III. Polycyclic Alcohols and their Derivatives.*

By W. KLYNE and W. M. STOKES.

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General rules are proposed regarding the molecular-rotation contributions of hydroxyl groups and derived functions in alicyclic compounds. These rules are based on the work of Stokes and Bergmann (*J. Org. Chem.*, 1952, **17**, 1194) and of Mills (*Chem. and Ind.*, 1953, 212). The rules are applied to triterpenoid alcohols and to steroid alcohols carrying hydroxyl groups in ring D.

The molecular-rotation contributions of hydroxyl and derived functions in the steroid side-chain are compared with those for simple aliphatic compounds.

THE previous papers in this series (Klyne, *J.*, 1952, 2916; 1953, 3072) have dealt chiefly with the contributions of ketonic and olefinic groupings to the molecular rotations of polycyclic compounds.

Stokes and Bergmann (*J. Org. Chem.*, 1952, **17**, 1194) have shown that certain general principles may be applied to the rotation contributions of hydroxy-, acetoxy-, and benzoyloxy-groups in steroids. They tried to apply Marker's empirical rules regarding the optical rotations of acyclic compounds (*J. Amer. Chem. Soc.*, 1936, **58**, 976) to steroids and reached the provisional conclusion that the steroid convention for formulæ was opposite to the glyceraldehyde convention.

Mills (*Chem. and Ind.*, 1953, 212) showed by reference to monoterpenoids, whose configurations have been reliably correlated with that of glyceraldehyde, that this application of Marker's rule to cyclic compounds is unjustified and leads to the wrong answer. He produced evidence from the rotations of saturated hydroxy-steroids and hydroxy-monoterpenoids (*loc. cit.*) and from those of their allylic analogues (*J.*, 1952, 4976) that the steroid and the glyceraldehyde convention are in agreement. Prelog and his colleagues (*Helv. Chim. Acta*, 1953, **36**, 308, 320, 325) have confirmed this conclusion by the method of asymmetric synthesis which they have applied to monoterpenoids, triterpenoids, and steroids. Klyne (*J.* 1952, 2916) had previously correlated the triterpenoids with the steroids.

The method of rotational analysis used by Stokes and Bergmann (*loc. cit.*) for steroid alcohols and their derivatives can be applied to triterpenoid alcohols in the light of the later work of Mills (*loc. cit.*, 1953). The results are with few exceptions consistent within themselves and with other evidence regarding the stereochemistry of the triterpenoids.

The value of empirical methods such as these is dependent on their wide applicability. It therefore seems desirable to summarise the data on triterpenoids to provide a firmer foundation for the use of the method in dealing with structural problems. Some further examples from the steroid field are also discussed.

A preliminary communication on this subject has been made (Klyne and Stokes, *Biochem. J.*, 1953, **55**, xxviii).

Conventions.—Molecular rotations and differences are given in parentheses. Values are all for the sodium D line and nearly all for chloroform as solvent. The symbols ΔOH, ΔOAc, and ΔOBz are used as by Klyne and by Stokes and Bergmann (*loc. cit.*). The symbols Δ_1 (ΔOAc − ΔOH) and Δ_2 (OBz − ΔOH) are used as by Barton and Jones (*J.*, 1944, 659).

PRINCIPLES

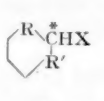
An asymmetric centre C* in a *cyclo*hexane ring system (I) may be represented as (II) where X is a substituent and R and R′ are the ring-members adjacent to C* together with their substituents. If C* is now represented as in (III) by a projection on to a plane at right angles to the bond C*–H, and seen from the side opposite to H (cf. Marker, *loc. cit.*)

* Part II, *J.*, 1953, 3072.

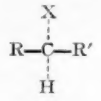
then, if X is hydroxyl, acetoxyl, or benzoyloxy, the magnitude and sign of the rotation contribution of the centre are dependent on the degree of alkyl substitution in R and R'.

(i) If R and R' are both CH_2, the rotation contribution of C* will be small, and attempts to predict its sign are unwise.

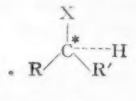
(ii) If R is $-CH_2{\cdot}C$ and R' is $-\overset{C}{\underset{C}{CH}}$ or $-\overset{C}{\underset{C}{C}}-C$ the rotation contribution of C* will be *negative* (and appreciable). Here the ordinal numbers of the substituents in the Marker system ($R < R' < X$) increase counter-clockwise.



(I)



(II)



(III)

(iii) If R is $-\overset{C}{\underset{C}{CH}}$ or $-\overset{C}{\underset{C}{C}}{\cdot}C$ and R' is $-CH_2{\cdot}C$, the rotation contribution of C* will be *positive* (and appreciable). Here the ordinal numbers in the Marker system increase in a clockwise direction ($R' < R < X$).

ΔOAc and ΔOBz values are generally greater than the corresponding ΔOH values; Δ_1 and Δ_2 values are therefore usually of the signs indicated by the above rules.

The rules do not apply generally to positions adjacent to a ring junction in *cis*-fused polycyclic systems. For example, some of the Δ values for the 6-position in steroids of the 5β-(A–B-*cis*-)series are anomalous. According to the rules it would be expected that Δ values of α- and β-substituents would be positive and negative respectively. The following values are taken from the tables of Barton and Klyne (*Chem. and Ind.*, 1948, 755).

	6α			6β		
	ΔOH	ΔOAc	Δ_1	ΔOH	ΔOAc	Δ_1
5α(*trans*)-Series	+ 55°	+210°	+155°	−50°	−110°	−60°
5β(*cis*)-Series	−100	− 87	+ 13	+ 7	− 62	−69

Similar rules may apply for substituents other than hydroxyl and its derivatives, but there is insufficient evidence to extend the principles at present. The data for 7-halogen-substituted steroids (see, *e.g.*, Henbest and Jones, *J.*, 1948, 1798; Schaltegger and Müllner, *Helv. Chim. Acta*, 1951, **34**, 1096), for 7-aminosteroids (Barnett, Ryman, and Smith, *J.*, 1946, 524; Sax and Bernstein, *J. Org. Chem.*, 1951, **16**, 1069), and for the menthylamines (Read, *Trans. Faraday Soc.*, 1930, **26**, 441; Read and Grubb, *J.*, 1934, **314**; McNiven and Read, *J.*, 1952, 153) would support this extension.

The above rules probably apply also to *cyclo*pentane rings; values in the steroid skeleton for $C_{(17)}$ (Stokes and Bergmann, *loc. cit.*) and for $C_{(16)}$ (see below, p. 1984) agree with the rules, but more examples are necessary.

Application of principles to triterpenoids

The rotational data for triterpenoid alcohols and their derivatives, which largely support the principles, are summarised in Table 1.

Positions Adjacent to a Bridgehead.—In the pentacyclic triterpenoids of the oleanane (IV), ursane (V), and lupane (VI) series (numbering according to Guider, Halsall, and Jones, *J.*, 1953, 3024), the positions 7, 11, and 16 should resemble steroid positions 4, 7, and 11 (see VII); ΔOH, ΔOAc, ΔOBz, Δ_1, and Δ_2 should be negative for α-substituents and positive for β-substituents.

Triterpenoid positions 1, 6, and 12 or 15 should resemble steroid positions 1, 6, and 12; here Δ values should be positive for α-substituents and negative for β-substituents. Rotation contributions in the lanostane (VIII; R = H) and eburicane (VIII; R = Me) series

TABLE I. *Δ Values for hydroxyl and related substituents in triterpenoids.*

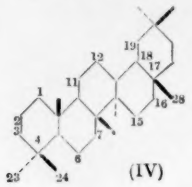
Position considered	Other groups	[M]D CH2 [a]	α-Substituents [M]D OH	α-Substituents [M]D OAc	α-Substituents Δ values OH	α-Substituents Δ values OAc	α-Substituents Δ values Δ1	β-Substituents [M]D OH	β-Substituents [M]D OAc	β-Substituents [M]D OBz	β-Substituents Δ values OH	β-Substituents Δ values OAc	β-Substituents Δ values OBz	β-Substituents Δ values Δ1	β-Substituents Δ values Δ2	Refs.
Oleanane series (IV).																
3	None	+41°	—	—	—	—	—	+77°	+99°	—	+36°	+58°	—	+22°	—	1
	12-Ene	+390	+311°	+174° [b]	−79°	−216°	−137°	+379	+384	+530°	−11 *	−6 *	+140°	+5	+151°	1
6	3β-OH, 12-ene, 28-CO_2Me	+348	—	—	—	—	—	+228	—	—	−120	—	—	—	—	2
	3β-OAc, ,, ,,	+348	—	—	—	—	—	+211	+142	—	−137	−206	—	−69	—	2
	3β-OAc, ,,	+384	—	—	—	—	—	+193	—	—	−191	—	—	—	—	2
11	3β-OH, 28-CH_2·OH	+30 [c]	—	—	—	—	—	+88	—	—	+58	—	—	—	—	3
	3β-OAc, 28-CH_2·OAc	+35 [c]	—	—	—	—	—	+168	+322	—	+133	+287	—	+154	—	3
12	3β-OH	+77	—	—	—	—	—	+436 [d]	—	—	+359	—	—	—	—	4
	3β-OAc	+99	—	—	—	—	—	—	+226	—	—	+227	—	—	—	4
16	3β-OAc, 12-ene	+384	+227 [e]	+58	−157	−326	−169	+406 [f]	+468	—	+22	+84	—	+62	—	5, 6, 7
	3β-OH, 12-ene	+379	+252	—	−127	—	—	+300	—	—	−79 *	—	—	—	—	5, 6, 7
Ursane series (V).																
3	12-Ene	+390	—	+182	—	−208	—	+358	+370	+498	−32 *	−20 *	+108	+12	+140	1, 8, 9
Lupane series (VI).																
1 [g]	None	−16 [h]	+163	+111 [i]	+179	+127 [i]	−52 [i] *	−126	−94	—	−110	−78	—	+32 *	—	10
3	None [j]	−16 [h]	—	−230	—	−214	—	−77	−9	+144	−61 *	+7	+160	+68	+251	10, 11
	20(29)-Ene	+115	—	—	—	—	—	+115	+201	+318	0	+86	+203	+86	+203	10, 11
Lanostane series (VIII).																
3	None	+145	—	—	—	—	—	+150	+194	—	+5	+49	—	+44	—	12, 13, 14, 15
	8-Ene	+272	—	—	—	—	—	+261	+273	+378	−11 *	+1	+106	+12	+117	12, 13, 14, 15
	8 : 24-Diene	+267	—	—	—	—	—	+258	+306	+392	−9 *	+39	+125	+48	+134	12, 13, 14, 15
7	3β-OAc, 11β-OH [k]	+113	—	—	—	—	—	—	+392	—	—	+279	—	—	—	12, 16
11	3β-OH [j]	+150	0	—	−150	—	—	+128	—	—	−22 *	—	—	—	—	12, 15, 17
	3β-OAc	+194	—	+69	—	−125	—	+113	—	—	−81 *	—	—	—	—	12, 15, 17
12	Four examples [l]	—	—	—	—	+288 to +322	—	—	—	—	—	—	—	—	—	18

* Anomalous. [a] At position considered. [b] Klyne, unpublished observation. [c] Estimated from values for erythrodiol and Δ(C:C)12. [d] Obtained from 12-ketone by reduction with sodium and amyl alcohol; presumably equatorial (12β-)hydroxyl. [e] Echinocystic acid derivatives. [f] Maniladiol. [g] Configurations allotted here (see p. 1980). [h] This value appears to be too positive; Δ(C:C)20(29) in all other lupene derivatives is about +190° (cf. Barton and Jones, *loc. cit.*). [i] Propionate, not acetate. [j] [M]D of 3α-BzO-compound is −176°; ΔOBz, −160°. [k] Acetoxyl and ketone groups at $C_{(7)}$ and $C_{(11)}$ show considerable vicinal action. [l] Derivatives of polyporenic acid A [3α : 12α-dihydroxyeburica-8 : 24(28)-dien-26-oic acid].

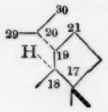
References: Many values are taken from the Tables given by Barton and Jones (*loc. cit.*) and Klyne (1952, *loc. cit.*). **1**, Ruzicka and Wirz, *Helv. Chim. Acta*, 1941, **24**, 248. **2**, Ruzicka, Jeger, Grob, and Hösli, *ibid.*, 1943, **26**, 2283. **3**, Barton and Holness, *J.*, 1952, 78. **4**, Picard, Sharples, and Spring, *J.*, 1939, 1045. **5**, Jeger, Montavon, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1124. **6**, Jeger, Nisoli, and Ruzicka, *ibid.*, p. 1183. **7**, Meyer, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 687. **8**, Ruzicka and Gubser, *ibid.*, 1945, **28**, 1054. **9**, Büchi, Jeger, and Ruzicka, *ibid.*, 1946, **29**, 442. **10**, Jeger, Montavon, Nowak, and Ruzicka, *ibid.*, 1947, **30**, 1869. **11**, Nowak, Jeger, and Ruzicka, *ibid.*, 1949, **32**, 323. **12**, Voser, Montavon, Günthard, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 1893. **13**, Ruzicka, Rey, and Muhr, *ibid.*, 1944, **27**, 472. **14**, Ruzicka, Denss, and Jeger, *ibid.*, 1945, **28**, 759. **15**, McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176. **16**, Cavalla and McGhie, *J.*, 1951, 834. **17**, Mijović, Voser, Heusser, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 964. **18**, Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457; cf. Roth, Saucy, Anliker, Jeger, and Heusser, *Helv. Chim. Acta*, 1953, **36**, 1908.

should follow the same pattern as in the other triterpenoids and steroids. Table 1 shows that, in general, agreement of the predicted signs with those found experimentally is good.

Configurations for 1-substituted triterpenoids (Jeger *et al.*, *Helv. Chim. Acta*, 1947, **30**, 1869) are allotted here on the basis of the ΔOH and ΔOAc values. These allocations are supported by the high positive rotation of lup-2-en-1α-yl propionate (+724°) (cf. Mills, *loc. cit.*, 1952; Klyne, *Helv. Chim. Acta*, 1952, **35**, 1224).


(IV)

(V)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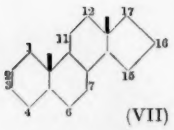
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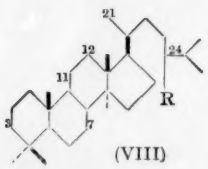
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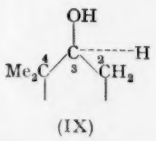

(IX)

Position **3**.—$C_{(3)}$ in steroids is flanked by two methylene groups and therefore shows very small Δ values (cf. Stokes and Bergmann, *loc. cit.*). $C_{(3)}$ in triterpenoids, however, is flanked by one methylene group and one CMe_2 group (IX) (3β-hydroxy-compound) and is therefore comparable with positions adjacent to a ring-junction. The Δ values for $C_{(3)}$ for saturated triterpenoids are rather larger than those for $C_{(3)}$ in steroids and their signs (β-groups chiefly positive, α-groups all negative) are in accordance with the principles stated above. Δ Values at $C_{(3)}$ are subject to much vicinal action by other parts of the triterpenoid molecule (cf. Barton and Jones, *loc. cit.*).

3α-Hydroxy-triterpenoids are sufficiently uncommon to warrant special attention. Halsall, Jones, and their colleagues have drawn attention to the large negative Δ_1 values for the 3-hydroxyl groups in polyporenic acid A (3α : 12α-dihydroxyeburica-8 : 24(28)-dien-26-oic acid; *J.*, 1953, 457, 3019) and in hydroxyelemadienic acid (*J.*, 1953, 4139). The epimeric 3β-hydroxy-compounds showed positive Δ_1 values (cf. also Gascoigne, Robertson, and Simes, *J.*, 1953, 1830).

Brein.—The unsaturated diol brein is known to be an urs-12-ene-3 : *x*-diol (Jeger, *Fortschr. Chem. org. Naturstoffe*, 1950, **7**, 1, see p. 57; references there). There has been some confusion regarding the configuration of the hydroxyl group at $C_{(3)}$. Two 3-epimeric hydroxy-*x*-ketones (breinonol A and B, Morice and Simpson, *J.*, 1942, 198; Büchi, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 442) can be obtained by Meerwein–Ponndorf reduction of the 3 : *x*-dione. Breinonol B must have the same configuration at $C_{(3)}$ as brein because it can also be obtained by oxidation of brein 3-monoacetate with chromic acid (Büchi *et al.*, *loc. cit.*). The same authors claimed that both breinonol acetates on Wolff–Kishner reduction gave " epi-α-amyrin " (urs-12-en-3α-ol) in rather poor yield, and therefore suggested that brein might be a 3α-hydroxy-triterpenoid. However, the catalytic reduction of breindione with platinum oxide in glacial acetic acid yields breinonol B; urs-12-en-3-one in similar circumstances gives the 3β-hydroxy-compound.

Consideration of molecular rotations (Table 2) shows clearly that brein (and breinonol B) are 3β-hydroxy-compounds and that breinonol A is 3α. The Δ_1 values at $C_{(3)}$ for brein and breinonol B agree well with that for urs-12-en-3β-ol (+12°), and that for breinonol A has a large negative value similar to those for 3α-ols (see Table 1). (Isolation of urs-12-en-3α-ol after Wolff–Kishner reduction of " breinonol B " may have been due to contamination of this with the isomer A.)

No conclusions can be drawn from rotations regarding the position or configuration of the second hydroxyl group, at *x*. The data are, however, consistent with its being a

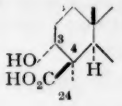
16β-hydroxyl group as in maniladiol (olean-12-ene-3β : 16β-diol), which accompanies brein in Manila elemi resin (cf. Morice and Simpson, *loc. cit.*, 1940).

TABLE 2. *Brein derivatives.*

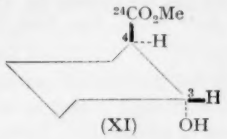
	Substituents		$[M]_D$		
	3	*x*	3-OH	3-OAc	Δ_1 at $C_{(3)}$
Brein	β-OH	OH	+292°	+324°	+ 32°
Breinonol B	β-OH	O	+211	+222	+ 11
Breinonol A	α-OH	O	+163	− 63	−226

References: Morice and Simpson, *loc. cit.*, and *J.*, 1940, 795; Büchi *et al.*, *loc. cit.*

α-Boswellic Acid (*3α-Hydroxyolean-12-en-24-oic Acid*, X).—Ruzicka and Wirz (*Helv. Chim. Acta*, 1940, **23**, 132; 1941, **24**, 248) showed that this acid has a 3α-hydroxyl group, and this is confirmed by the reduction of the corresponding 3-ketone by sodium and alcohol to an epimeric (3β-hydroxy-)acid (Meyer, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 672). Evid-



(X)



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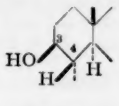
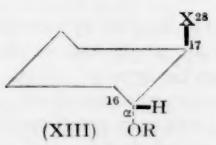


(XII)

ence for the β-orientation of the carboxyl group at $C_{(4)}$ in α-boswellic acid is given by Vogel, Jeger, and Ruzicka (*ibid.*, 1951, **34**, 2321). The Δ values of α-boswellic acid and its derivatives support the allocation of a 3α-configuration; for the methyl esters ΔOH, −80°; ΔOAc, −268°; Δ_1, −188°.

These values are of interest because they show that there is relatively little vicinal action between 4β-methoxycarbonyl groups and 3α-hydroxyl or -acetoxyl groups. Barton and Jones (*loc. cit.*), writing long before anything was known about the stereochemistry of ring A, suggested that hydrogen-bonding between such groups might occur and might be responsible for abnormal Δ values. It is now clear that 3α- and 4β-substituents, being both axial and antiparallel (XI) would be most unfavourably placed for hydrogen bonding. There is, however, serious vicinal action between a 4β-methoxycarbonyl group and a 3-keto-group (ΔC:O for the keto-ester from α-boswellic acid is −114°; standard value for olean-12-en-3-one, +64°). Similar problems in steroid α-ketols have been discussed recently by Norymberski (*J.*, 1954, 762).

Data for the various 3 : 23- and 3 : 24-diols are too incomplete to justify a full discussion, but in general it seems that the ΔOH and ΔOAc values for hydroxyl groups at $C_{(23)}$ and $C_{(24)}$ are small; furthermore the effect of these groups on the rotation contributions of similar groups at $C_{(3)}$ is small.



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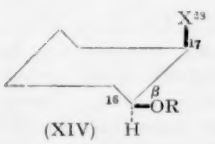

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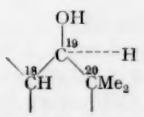


(XV)

β-Boswellic Acid.—This acid is almost certainly the ursane analogue of α-boswellic acid (3α-hydroxyurs-12-en-24-oic acid). There are serious discrepancies in the literature in the rotations quoted for β-boswellic acid and its derivatives (see Elsevier's "Encyclopædia of Organic Chemistry," 1940, Vol. XIV, pp. 559—561; and 1953, Supplement, p. 1087 S). However, the Δ_1 values are all large negative ones, indicating a 3α-hydroxyl group.

24-Nor-compounds.—Δ_1 Values for 24-nor-3β-hydroxy-compounds (XII) show the expected positive values; hedragenin (3β-hydroxy-24-norolean-12-en-28-oic acid), +82°; nor-β-amyrin (24-norolean-12-en-3β-ol) +29°.

The "nor-β-boswellenol" of Simpson and Williams (*J.*, 1938, 686, 1712) has Δ_1 (+52°) and must therefore be 24-norurs-12-en-3β-ol (cf. Barton and Jones, *loc. cit.*). The stereo-

isomeric " nor-β-boswellanonols " of the same authors (m. p.s 182—183° and 231—232°) have Δ_1 values of (+86°) and (−65°) and must therefore be 3β- and 3α-hydroxy-compounds respectively.

Position 16.—The Δ_1 values at this position are highly characteristic, those for α- and β-substituents being large negative and positive values respectively, as predicted by the rules. Since 3 : 16 : 28-trisubstituted compounds are common in Nature it is of interest that Δ_1 values at $C_{(16)}$ are not greatly affected by substituents at $C_{(28)}$.

The stereochemical relations between substituents at $C_{(16)}$ and $C_{(28)}$ are similar to those at $C_{(3)}$ and $C_{(24)}$ discussed on p. 1983. The following are Δ_1 values for representative compounds :

Group X at $C_{(28)}$	CH_3	CH_2·OH	CHO	CO_2H
16α-Series (XIII)	−194°	−297°	—	−232°
16β-Series (XIV)	+138	+175	+228°	—

References : Morice and Simpson, *J.*, 1940, 795; Margot and Reichstein, *Pharm. Acta Helv.*, 1942, **17**, 113; Jeger, Montavon, and Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1124; Jeger, Nisoli, and Ruzicka, *ibid.*, p. 1183; Jeger, Bischof, and Ruzicka, *ibid.*, 1948, **31**, 1319; Bischof and Jeger, *ibid.*, p. 1760; Djerassi, McDonald, and Lemin, *J. Amer. Chem. Soc.*, 1953, **75**, 5940; Djerassi, Geller, and Lemin, *Chem. and Ind.*, 1954, 161.

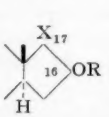
These Δ values are all {$[M_D]$ (fully acetylated compound) *minus* $[M]_D$ (alcohol)}, and most of the compounds have a 3β-hydroxyl group as well as that at $C_{(16)}$. Changes due to acetylation of 3β- and 28-hydroxyl groups are, however, small; Δ_1 for 3β-hydroxyl is +5° (see Table 1). Δ_1 for 28-hydroxyl is about −30° [olean-12-en-3β : 28-diol (erythrodiol) +330°; 3-acetate +344°; 3 : 28-diacetate, +310°].

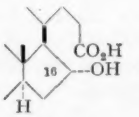
Djerassi, Geller, and Lemin (*loc. cit.*) have drawn attention to the fact that Δ(16β-acetoxy *minus* 16α-acetoxy) is constant in spite of substitution at $C_{(28)}$. (The authors are indebted to Prof. C. Djerassi for a copy of this paper before publication.)

Position 19.—This position is peculiar in that it is flanked in the oleanane series by a tertiary and a quaternary carbon atom (XV; 19β-OH); the rules therefore cannot be applied. Δ(OH) values for α- and β-substituents in the 18α-(D–E-*trans*)-series are both negative, α being greater than β (see Klyne, Part II, *loc. cit.*, Table 11).

Further applications to steroids

Stokes and Bergmann (*loc. cit.*) have discussed the rotational contributions of hydroxyl and related groupings in rings A, B, and C of the steroid nucleus. Groups in ring D and in the side-chain will be considered here.

(XVI) 



(XVII)

Position 16.—In C_{19} steroids (XVI; X = H) this position is flanked by two methylene groups, and small Δ values would be expected. No values are at present available, but values for 2-substituted A-norsteroids, which are of enantiomeric type (cf. Klyne, Part I, *J.*, 1952, 2916), may be considered instead. The epimeric A-norandrostan-2-ols (Ruzicka, Meister, and Prelog, *Helv. Chim. Acta*, 1945, **28**, 1651) both have very small rotations (2α, +5°; 2β, +8°). A-Norandrostane is not known, but since A-norcholestane and cholestane have almost identical rotations (cf. Klyne, *loc. cit.*, Table 4), A-norandrostane would be expected to have a negligible rotation, like androstane (+5°). The ΔOH values for the 2-hydroxyl groups are therefore almost zero.

In C_{21} steroids position 16 is flanked by one methylene group and one tertiary carbon atom (XVI; X = CHMe·OR') and, as expected, Δ values are considerable. The values for α-substituents are negative and for β-substituents positive, in agreement with the rules stated above (p. 1980).

A summary, including Δ values for 16α- and 16β-acetoxyl and 16α-methoxyl groups, is given by Fukushima and Gallagher (*J. Amer. Chem. Soc.*, 1951, **73**, 196: see also Hirschmann and Hirschmann, *J. Biol. Chem.*, 1950, **184**, 259; Hirschmann, Hirschmann, and

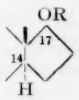
Farrel, *J. Amer. Chem. Soc.*, 1953, **75**, 4862; Vischer, Schmidlin, and Wettstein, *Helv. Chim. Acta*, 1954, **37**, 321). Δ(OH)16α is −64° for 5α-pregnane-3β : 16α : 20β-triol (Brooks, Klyne, Miller, and Paterson, *Biochem. J.*, 1952, **51**, 694); Δ(O·CH_2Ph)16α is −194° (Hirschmann, Hirschmann, and Daus, *J. Amer. Chem. Soc.*, 1952, **74**, 539).

Some of these values are subject to vicinal action by the substituents at $C_{(20)}$, but they include examples from both 20α- and 20β-substituted compounds.

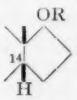
The bile acid, pythocholic acid, isolated by Haslewood and Wootton (*Biochem. J.*, 1950, **47**, 584; 1951, **49**, 67) has been shown by these authors to be a 3α : 12α : *x*-trihydroxycholanic acid where *x* is 16 (or 15). Position 15 is excluded since the *x*-oxo-derivatives show large negative rotational contributions, which are compatible with that from a 16-ketone but not with that from a 15-ketone. Δ(C:O)15 is (+106°) (Barnes, Barton, and Laws, *Chem. and Ind.*, 1953, 616; Barton and Laws, *J.*, 1954, 52). The Δ(OH) value for the third hydroxyl (*x*) is +123° − 195° = −72°. This negative value indicates a 16α-hydroxyl group (XVII).

Rotational contributions at $C_{(16)}$ in the cardiac aglycones and toad poisons cannot be treated as reference values because of vicinal action by the unsaturated lactone rings in the side chain and by the 14β-hydroxyl group.

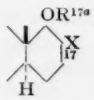
Position 17.—The data collected by Stokes and Bergmann (*loc. cit.*) show that for 17-substituted steroids of the normal C–D-*trans*-series (*e.g.*, XVIII), the general principles



(XVIII)



(XIX)



(XX)

stated on p. 1980 are applicable, although the substituents are in a *cyclo*pentane and not a *cyclo*hexane ring. Values are now available for 17-epimeric steroids of the 14β-(C–D-*cis*-) series (XIX) (St. André, MacPhillamy, Nelson, Shabica, and Scholz, *J. Amer. Chem. Soc.*, 1952, **74**, 5506). The values for $\{[M]_D(17\beta) - [M]_D(17\alpha)\}$ are of the expected sign. Since the corresponding compounds unsubstituted at $C_{(17)}$ are unknown, ΔOH and ΔOAc values cannot be calculated.

	$[M]_D$ 17α	$[M]_D$ 17β	Δ(17β−17α)
14β-Androstane-3β : 17-diol	+105°	+111°	+ 6°
,, ,, diacetate	+ 87	+132	+45
(14α)-Androstane-3β : 17-diol	− 29	+ 12	+41
,, ,, diacetate	− 67 *	0	+67

* Estimated from values in the Tables of Barton and Klyne (*Chem. and Ind.*, 1948, 755) and the value for 17α-acetoxy-5β-androstan-3α-ol (Gallagher and Kritchevsky, *J. Amer. Chem. Soc.*, 1950, **72**, 882).

Position 15.—The above data seem to justify the application of the rules to the 15(?α)-substituted steroids recently prepared by Barton and Laws (*J.*, 1954, 52). (The authors are grateful to Prof. D. H. R. Barton, F.R.S. for an advance copy of this paper.) These compounds show ΔOAc +184°, and ΔOBz +365°, which support the allotment of the 15α-configuration.

Position 17α *in* D-*Homosteroids*.—The Δ values at this position (XX; X = H) are in accordance with the rules above (except for the one acetate value), α-substituents being negative and β-substituents positive. The indices α and β are allotted according to Goldberg, Sicé, Robert, and Plattner (*Helv. Chim. Acta*, 1947, **30**, 1441). Representative values are as follows:

Position	ΔOH	ΔOAc	ΔOBz	Δ_1	Δ_2
17*aα*	−38°	—	−190°	—	−152°
17*aβ*	+90	−27° *	+321	−117° *	+231

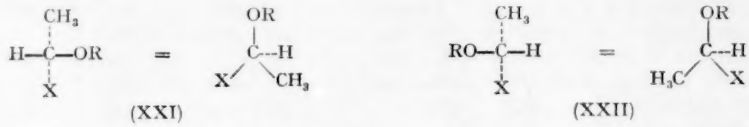
* Anomalous.

References: Goldberg *et al.*, *loc. cit.*; Goldberg and Wydler, *Helv. Chim. Acta*, 1943, **26**, 1142.

For the 17*a* position in ursanediol derivatives (17α-methyl-3β : 17*a*β-diol series (XX; X = Me), Brooks *et al.* (*loc. cit.*) give Δ_1 −104°, Δ_2 +100°. Here the 17*a*-position somewhat resembles 19 in the 18α-oleanane series (cf. p. 1984).

THE STEROID SIDE CHAIN

Now that the stereochemistry of the steroid nucleus has been related to glyceraldehyde,* and the stereochemistry of $C_{(20)}$ to $C_{(17)}$ (Fieser and Fieser, *Experientia*, 1948, **4**, 285; for a recent review see Klyne, *Chem. and Ind.*, 1951, 426; also Prelog and Tsatsas, *Helv. Chim. Acta*, 1953, **36**, 1178), it seems appropriate to compare the rotational contributions of $C_{(20)}$ and other side-chain centres with those of the corresponding atoms in simple aliphatic compounds.



(XXI) (XXII)

Position 20.—The contributions of hydroxyl and derived groups at $C_{(20)}$ may be compared with the rotations of other alcohols where the CH·OH group is flanked by a methyl group and a tertiary carbon atom X (Table 3). It is seen that the contributions of $C_{(20)}$ in the steroids, where X is a substituted *cyclo*pentyl group, are of the same sign as the rotations of the simpler *iso*propyl and *cyclo*hexyl compounds.

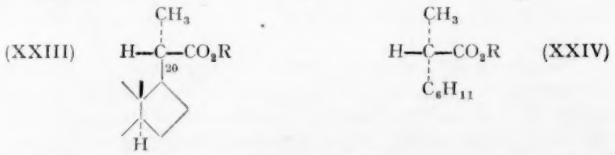
TABLE 3. *Molecular rotations and Δ values for $C_{(20)}$ and simpler reference compounds.*

Values shown in the columns headed OBz are for benzoates in the steroid series and for hydrogen phthalates in the aliphatic compounds. Values for the benzoates and hydrogen phthalates of the same alcohol are very similar (Kenyon and Pickard, *J.*, 1915, **107**, 121).

			Type XXI			Type XXII			
Value	X	OR:	OH	OAc	OBz	OH	OAc	OBz	Refs.
$[M]_D$	$CHMe_2$		+ 4°	—	+ 98°	− 4°	—	− 98°	a
$[M]_D$	*cyclo*Hexyl		+ 7	− 5°	+150	− 7	+ 5°	−150	a, b
			← (20α) →			← (20β) →			
Δ for $C_{(20)}$	$_{17}C(H)$		+15	−22	+130	−43	+68	−150	c

References: a, See summary in Freudenberg, "Stereochemie," Vol. II, facing p. 696, Deuticke, Leipzig and Vienna. b, Levene and Harris, *J. Biol. Chem.*, 1936, **113**, 55. c, ΔOH and ΔOAc from Barton and Klyne, *loc. cit.* ΔOBz from Brooks, Klyne, and Miller, *Biochem. J.*, 1953, **54**, 212. These benzoate contributions are subject to much vicinal action.

It therefore seems justified to apply these values to deduce the configurations of carbinol groups in similar structures. This is virtually the same as applying Marker's rule in its original form for acyclic compounds.



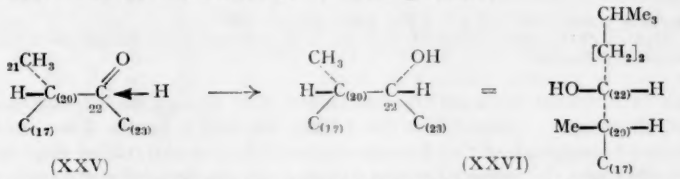
(XXIII) (XXIV)

The bisnorcholanic acids (XXIII) and their 20-epimers may now be compared with the α-*cyclo*hexylpropionic acids [XXIV, (+)-acid] recently described by Cram and Greene (*J. Amer. Chem. Soc.*, 1953, **75**, 6005). $[M]_D$ of (XXIV) is +30°; Δ(XXIV − its enantiomer) is therefore +60°. Δ Values for the 20-*n*-bisnorcholanic esters (XXIII; R = Me) *minus* the corresponding 20-*iso*-bisnorcholanic esters are, with one exception, positive (+103°, +72°, +181°, −60°, +36°, +25°) (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 3rd edn., 1949, p. 418; Sorkin and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 1631; 1945, **28**, 875).

Position 22.—Fieser and Wei-Yuan Huang (*J. Amer. Chem. Soc.*, 1953, **75**, 5356) have reduced 22-oxocholestan-3β-ol with lithium aluminium hydride and obtained (apparently)

* A direct correlation of the configuration of $C_{(20)}$ with that of asymmetric carbon atoms in the branched-chain aliphatic series has recently been achieved by Cornforth, Youhotsky, and Popják (*Nature*, 1954, **173**, 536) and by Riniker, Arigoni, and Jeger (*Helv. Chim. Acta*, 1954, **37**, 546).

only one of the two possible cholestane-3β : 22-diols. Application of Cram's rule of steric control of asymmetric induction (*ibid.*, 1952, **74**, 5828) to a 22-oxo-steroid (XXV) indicates that the 22" β "-isomer (XXVI) should preponderate in the reduction products. (The index " β " is allotted according to the convention proposed by Plattner for side-chain isomers, *Chem. and Ind.*, 1951, SN 1; *Helv. Chim. Acta*, 1951, **34**, 1693. This convention is not generally accepted; indices are therefore given in quotation marks.) The cholest-5-ene-3β : 16β : 22 : 26-tetrol obtained by Sandoval, Romo, Rosenkranz, Kaufmann, and Djerassi (*J. Amer. Chem. Soc.*, 1951, **73**, 3820) by reduction of the corresponding 16 : 22-dione can therefore also be allotted the 22" β "-configuration.

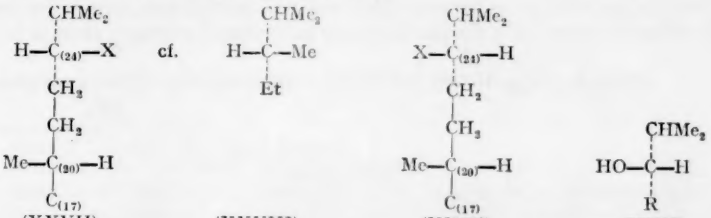


(XXV) (XXVI)

Stabursvik (*Acta Chem. Scand.*, 1953, **7**, 1220) has isolated from *Narthecium ossifragum* Huds. a cholest-5-ene-3β : 22ξ-diol, which on catalytic hydrogenation yields a saturated diol different from Fieser's 3β : 22" β "-diol. Stabursvik's natural product must therefore be the 22" α "-isomer.

The " rule of shift " cannot be applied at present to the molecular rotations of the cholestane-3β : 22-diols and their derivatives because adequate reference values for branched chain alcohols of the type R·$[CH_2]_2$·CH(OH)·CHMeR′ are not available.

Position 24.—*Alkyl substituents.* The application of Marker's rule to $C_{(24)}$ has been discussed by Stokes and Bergmann (*J. Org. Chem.*, 1951, **16**, 1817). In view of the confusion which has arisen regarding the relation of steroids to glyceraldehyde, it seems desirable to indicate projection formulæ for the 24-substituted hydrocarbons (XXVII, XXIX) in the light of the latest knowledge. The reference compound (XXVIII) has (+28°) (Levene and Marker, *J. Biol. Chem.*, 1935, **111**, 299).



(XXVII) (XXVIII) (XXIX) (XXX)

24"α"-Series (formerly 24*a*)
Campestanol, X = Me
Poriferastanol, X = Et

24"β"-Series (formerly 24*b*)
Ergostanol, X = Me
Stigmastanol, X = Et

Hydroxy-compounds. Ercoli, Di Frisco, and de Ruggieri (*J. Amer. Chem. Soc.*, 1953, **75**, 3289; *Gazzetta*, 1953, **83**, 78) have isolated from brain tissue a cholest-5-ene-3β : 24-diol (cerebrostenediol) and have synthesised this compound and its 24-epimer. Comparison of the molecular rotations of these compounds with reference values for *n*-alkyl*iso*propylcarbinols permits the allotment of configurations at $C_{(24)}$. The natural isomer (ξ^1) is thus shown to be 24" β " (XXIX; X = OH) (Plattner convention).

$[M]_D$ Values for *n*-alkyl*iso*propylcarbinols of the type (XXX) are: R = Et −17°, Pr^n −27°, Bu^n −36°, C_5H_{11} −38° (Freudenberg, *op. cit.*). If, in accordance with Stokes and Bergmann's suggestions (*loc. cit.*, 1951), the steroid nucleus *plus* side-chain as far as $C_{(23)}$ is considered as being similar to an ethyl group, the 24-hydroxyl compounds which show negative ΔOH values (the natural series) must be of the same enantiomeric type as (XXX).

No clear evidence can be obtained from the rotations of the acetates and benzoates of the $C_{(24)}$-isomers, because the acetates of the simple optically active carbinols (XXX) are

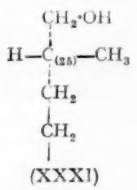
unknown, and the phthalates (= benzoates) show a change in sign of rotation between (XXX, R = Et; phthalate −10°) and (XXX, R = Pr^n; phthalate +22°).

	$[M]_D$				
	24-CH_2	24-CH·OH "α" (epi)(ξ^2)	24-CH·OH "β" natural (ξ^1)	Δ OH "α"	Δ OH "β"
Cholest-5-en-3β-ol	−151°	−108°	−195° *	+43°	−44°
Cholestan-3β-ol	+ 89	—	+ 97 †	—	+ 8
Cholest-4-en-3-one	+342	+375	+319	+33	−23

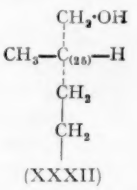
* Hey, Honeyman, and Peal (*J.*, 1952, 4836) give − 160°.

† All values in chloroform, except for this, which is in dioxan; the anomalous Δ value is probably due to a solvent difference.

Position 25.—Recent work on the stereochemistry of $C_{(25)}$ in the sapogenins (Scheer, Kostic, and Mosettig, *J. Amer. Chem. Soc.*, 1953, **75**, 4871; James, *Chem. and Ind.*, 1953, 1388) permits an independent check on the applicability of the rule of shift to positions in the steroid side chain, by using reference values from simple aliphatic compounds. These authors have shown that $C_{(25)}$ in dihydrosmilagenin (and the corresponding derivatives of tigogenin and hecogenin) must be represented as in (XXXI) (Fischer projection), whilst



(XXXI)



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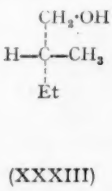

(XXXIII)

$C_{(25)}$ in dihydrosarsasapogenin is as in (XXXII). (These may be called 25*D*- and 25*L*-methyl compounds, following Linstead, Lunt, and Weedon, *J.*, 1950, 3333.)

If the rotation differences between 25*D*- and 25*L*-methyl compounds are compared with the molecular rotations of a simple α-methyl substituted primary alcohol (*e.g.*, 2-methyl-

TABLE 4. $C_{(25)}$-*Methyl-substituted compounds and simple analogues.*

	Group at $C_{(26)}$	$[M]_D$ *D* series	$[M]_D$ *L* series	Δ (*D* − *L*)
Genin derivatives.				
ψ-Genin [furost-20(22)ene-3β : 26-diol]	CH_2·OH	+100°	+ 50°	+50°
Dihydrogenin (furostan-3β : 26-diol)	CH_2·OH	+ 13	− 17	+30
Dihydrogenin diacetate	CH_2·OAc	− 5	− 15	+10 *
Dihydrogenin dibenzoate	CH_2·OBz	+ 12	+ 19	− 7
ψ-Genin bis-3 : 5-dinitrobenzoate	CH_2·OAcyl	+116	+177	−61
Aliphatic analogues (XXXIII).				
2-Methylbutanol	—	+ 5	− 5	+10
,, acetate	—	− 4	+ 4	− 8
,, hydrogen 3-nitrophthalate	—	−17	+17	−34

* Anomalous. References: Derivatives of genins, Scheer *et al.*, *loc. cit.* 2-Methylbutanol and derivatives, Marckwald and McKenzie, *Ber.*, 1901, **34**, 485. Guye and Chavanne, *Bull. Soc. chim.*, 1896, **15**, 280; Guye, *ibid.*, 1901, **25**, 549.

butanol, XXXIII) (see Table 4), the signs of the Δ values are as expected in all cases but one.

We are indebted to Professor Werner Bergmann (Yale) for helpful discussions.

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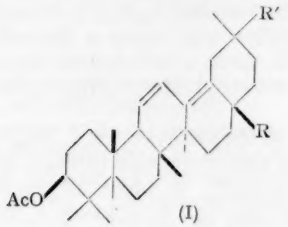
The Structure of the Acetate $C_{32}H_{46}O_5$ (O_5 *Acetate*) *derived from* β-*Amyrin.*

By L. C. McKean and F. S. Spring.

[Reprint Order No. 5084.]

The behaviour of the O_5 acetate with alkali has been studied and the nature of the products has been established; a formula (VI) is proposed for the O_5 acetate.

For a number of years it has been known that oxidation of oleana-11 : 13(18)-dienyl acetate (I; R = R′ = Me) with chromic acid gives, in high yield, an acetate, $C_{32}H_{46}O_5$ (O_5 acetate). The O_5 acetate is also obtained as a major product of the oxidation of 11-oxo-olean-12-enyl acetate (II; R = Me) or of 11-oxo-oleana-12 : 18-dienyl acetate (III; R = Me) with selenium dioxide and of olean-13(18)-enyl acetate (IV; R = R′ = Me) with chromic acid. Compounds directly related to the O_5 acetate are obtained by the same methods from corresponding derivatives of oleanolic acid and glycyrrhetic acid. Oxidation of methyl 11-oxo-olean-12-enolate acetate (II; R = CO_2Me) with selenium



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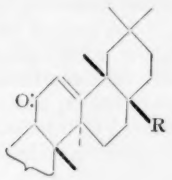

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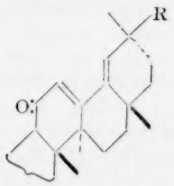

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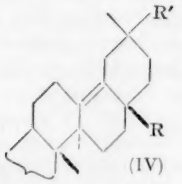

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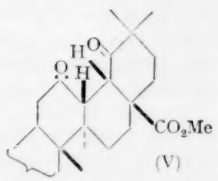


(V)

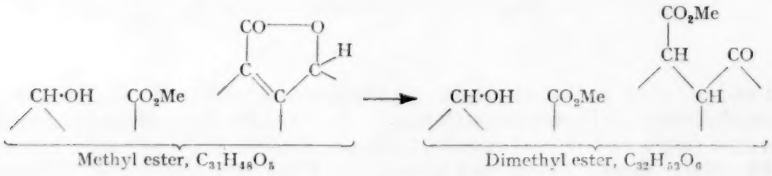
dioxide and of either methyl oleana-11 : 13(18)-dienolate acetate (I; R = CO_2Me, R′ = Me) or methyl olean-13(18)-enolate acetate (IV; R = CO_2Me, R′ = Me) with chromic acid gives in each case a methyl ester acetate, $C_{33}H_{46}O_7$ (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1236; Mower, Green, and Spring, *J.*, 1944, 256; Jeger, Norymberski, and Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 1532). The methyl ester acetate $C_{33}H_{46}O_7$ has been obtained by oxidation of methyl 12 : 19-dioxo-oleananolate acetate (V) with selenium dioxide (Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751). Oxidation of the glycyrrhetic acid derivatives, methyl oleana-11 : 13(18)-dienol-30-ate acetate (I; R = Me, R′ = CO_2Me) and methyl olean-13(18)-enol-30-ate acetate (IV; R = Me, R′ = CO_2Me) with chromic acid and of methyl 11-oxo-oleana-12 : 18-dienol-30-ate acetate (III; R = CO_2Me) with selenium dioxide gives, in each case, a methyl ester acetate isomeric with that obtained from the named oleanolic acid derivatives (Jeger, Norymberski, and Ruzicka, *loc. cit.*). The nature of the O_5 acetate and its related compounds has not been established or even the subject of conjecture and during the period in which the structure of the β-amyrin–oleanolic acid group of triterpenoids has been established beyond peradventure the formation and structure of this well-defined group of oxidation products has remained an enigma.

The O_5 acetate gives a faint yellow colour with tetranitromethane and its spectrum shows a broad band with maximum at approximately 2300 Å (ε 3000) together with a low-intensity inflection at 3000 Å. It does not contain a free hydroxyl group or react with

carbonyl reagents although the presence of a carbonyl group is suggested by the absorption spectrum. Apart from suffering simple hydrolysis of the $C_{(3)}$-acetoxy-group, the O_5 acetate is stable to mineral acid. With alkali, however, the O_5 acetate is profoundly changed. In aqueous alkali, an amorphous neutral fraction is obtained, acetylation of which gives a homogeneous acetate formulated by Mower *et al.* (*loc. cit.*) as $C_{33}H_{46}O_5$ (or a near homologue) and by Jeger *et al.* (*loc. cit.*) as $C_{30}H_{46}O_4$. As a minor product of the action of alkali on the O_5 acetate Jeger *et al.* (*loc. cit.*) obtained a monobasic acid, $C_{29}H_{46}O_5$, which showed a strong absorption maximum at 2270 Å (log ε 4·26).

We have re-examined the behaviour of the O_5 acetate with alkali. Treatment of the O_5 acetate with methanolic potassium hydroxide, with exclusion of water, gives in high yield a methyl ester, $C_{31}H_{48}O_5$, which gives the corresponding acetate, $C_{33}H_{50}O_6$. In contrast to the parent O_5 acetate, the methyl ester shows strong absorption at 2250 Å (ε *ca.* 15,000) and it gives a positive Légal test although the colour with the nitroprusside reagent develops slowly; these properties suggest that the methyl ester contains an $\alpha\beta$-unsaturated lactone group. Hydrolysis of the O_5 acetate by aqueous-alcoholic alkali again gave an amorphous neutral fraction, together with a crystalline acid. Acetylation of the neutral fraction yielded a crystalline acetate, $C_{31}H_{48}O_4$; this is identical with the acetate obtained by the same method by Mower *et al.*, and by Jeger *et al.* Alkaline hydrolysis of the acetate gives the corresponding (crystalline) alcohol, $C_{29}H_{46}O_3$, reacetylated to the parent acetate, $C_{31}H_{48}O_4$. Analysis of the crystalline acid, which is identical with that obtained by Jeger *et al.*, agrees with $C_{30}H_{46}O_5$. It shows a well-defined absorption band at 2260 Å (ε 12,700) and with diazomethane gives a methyl ester, $C_{31}H_{48}O_5$, identical with the product of methanolysis of the O_5 acetate.

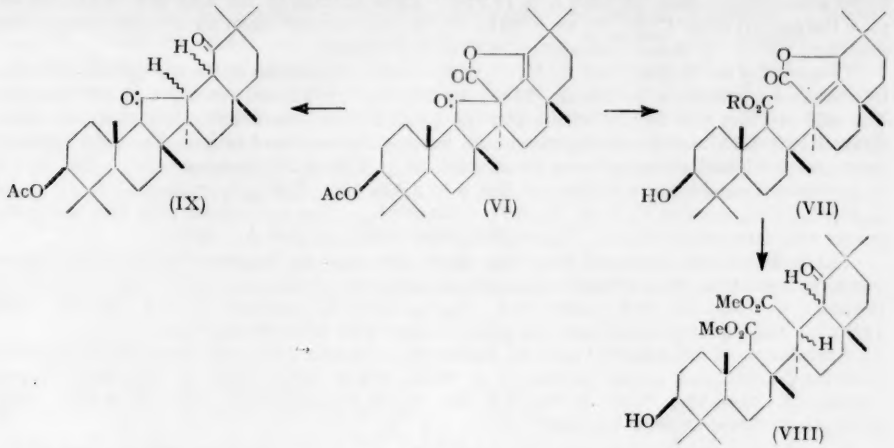
The presence of an $\alpha\beta$-unsaturated lactone grouping in the methyl ester, $C_{31}H_{48}O_5$, was confirmed by vigorous alkaline hydrolysis which gave an amorphous acid product, methylation of which yielded a crystalline dimethyl ester, $C_{32}H_{52}O_6$, in which all the oxygen functions have been characterised. Acetylation of the dimethyl ester yields a dimethyl ester acetate, $C_{34}H_{54}O_7$. The dimethyl ester and its acetate contain an isolated carbonyl group the presence of which was established by low-intensity absorption at 2800 Å. This behaviour of the methyl ester, $C_{31}H_{48}O_5$, with alkali is characteristic of $\alpha\beta$-unsaturated lactones (Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, **6**, 273) and establishes the relation depicted below.



These considerations lead us to the view that (VII; R = Me) is the formula for the methyl ester, $C_{31}H_{48}O_5$, and consequently, the acid, $C_{30}H_{46}O_5$, is (VII; R = H) and the dimethyl ester, $C_{32}H_{52}O_6$, is (VIII). Accordingly the O_5 acetate is represented as a $\beta\gamma$-unsaturated lactone (VI) and support for this formula was forthcoming from the infra-red absorption spectrum of the related alcohol, $C_{30}H_{44}O_4$ (Mower *et al.*, *loc. cit.*), which was examined by Dr. A. R. H. Cole, whom we thank. In carbon tetrachloride the alcohol shows two carbonyl bonds at 1745 (5-membered ring ketone) and at 1781 cm.$^{-1}$ ($\beta\gamma$-unsaturated γ-lactone) together with an ethylenic band at 1692 cm.$^{-1}$.

The acetate, $C_{31}H_{48}O_4$, obtained from the O_5 acetate (VI) by treatment with *aqueous* alkali (followed by acetylation) is considered to be the diketone (IX), the formation of which has involved rupture of the $\beta\gamma$-lactone group in (VI) followed by decarboxylation. Some support for this formula is to be found in the optical properties of the acetate, $C_{31}H_{48}O_4$, and of the corresponding alcohol, $C_{29}H_{46}O_3$. In the ultra-violet region, the acetate shows only low-intensity carbonyl absorption at 2900 Å. The infra-red absorption spectrum of the alcohol, $C_{29}H_{46}O_3$, for which we are greatly indebted to Dr. G. D. Meakins, shows two well-defined peaks in the carbonyl region, at 1725 and 1706 cm.$^{-1}$. Although

the peak at 1725 cm.$^{-1}$ is decidedly low for a carbonyl group in a 5-membered ring, the presence of two isolated carbonyl groups appears well established.



Experimental

Rotations were measured in chloroform at 15—22° and ultra-violet absorption spectra were determined in ethanol solution.

Treatment of the O_5 *Acetate with Aqueous-methanolic Alkali.*—The O_5 acetate (1·1 g.) was heated under reflux for 3 hr. with a solution of potassium hydroxide (5 g.) in water (10 c.c.) and methanol (90 c.c.). The mixture was diluted with water and extracted with ether, to yield a neutral fraction. The aqueous alkaline phase was acidified and extracted with ether, to give an acid fraction. The neutral fraction, which did not crystallise, was acetylated with pyridine and acetic anhydride at 100°. The acetate, $C_{31}H_{48}O_4$, separated from methanol–acetone as needles (660 mg.), m. p. 259·5—260·5°, $[\alpha]_D$ +158° (*c*, 0·9). It does not give a colour with tetranitromethane (Found: C, 76·6; H, 9·85. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%). Hydrolysis of the acetate by refluxing 5% ethanolic potassium hydroxide for 3 hr. gave the *alcohol*, $C_{29}H_{46}O_3$, which separated from aqueous methanol as needles, m. p. 102—103°, $[\alpha]_D$ +147° (*c*, 1·5) (Found: C, 76·3; H, 10·7. $C_{29}H_{46}O_3,CH_3{\cdot}OH$ requires C, 75·9; H, 10·6%). Acetylation of the alcohol (acetic anhydride–pyridine at 100°) gave the parent acetate, $C_{31}H_{48}O_4$, which separated from methanol–acetone as needles, m. p. and mixed m. p. 259·5—260·5°, $[\alpha]_D$ +154° (*c*, 1·0).

The acid fraction was crystallised from acetone–light petroleum, to give the *acid*, $C_{30}H_{46}O_5$ (50 mg.), m. p. 272—274° (279—281° *in vacuo*), $[\alpha]_D$ −36° (*c*, 1·3) (Found: C, 74·2; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%). Light absorption: Max. at 2260 Å (ε 12,700).

Treatment of the O_5 *Acetate with Methanolic Potassium Hydroxide.*—The O_5 acetate (1·78 g.) was heated under reflux for 2 hr. with potassium hydroxide (1·7 g.) in absolute methanol (34 c.c.). The mixture was diluted with water and extracted with ether to give a neutral fraction; acidification of the aqueous alkaline phase with dilute hydrochloric acid followed by extraction with ether gave an acid fraction. The neutral fraction was digested with aqueous methanol, and the crystalline solid recrystallised from the same solvent, to yield a *methyl ester* as cubes (765 mg.), m. p. 234—236°, $[\alpha]_D$ −46° (*c*, 1·6) (Found: C, 74·6; H, 9·6; OMe, 6·0. $C_{30}H_{45}O_4{\cdot}OCH_3$ requires C, 74·7; H, 9·7; OMe, 6·2%). Light absorption: Max. at 2250 Å (ε 15,500). The methyl ester does not give a colour with tetranitromethane but it slowly gives a positive Légal test.

The *methyl ester acetate* was obtained from the methyl ester by using pyridine and acetic anhydride at 100°. It separated from aqueous methanol as long prisms, m. p. 192—194°, $[\alpha]_D$ −33° (*c*, 1·2) (Found: C, 73·3; H, 9·3. $C_{33}H_{50}O_6$ requires C, 73·0; H, 9·3%). Light absorption: Max. at 2240 Å (ε 15,700).

The first mother-liquor from the methyl ester was evaporated and the amorphous residue acetylated (acetic anhydride–pyridine at 100°). The product crystallised from methanol–acetone, to yield the acetate, $C_{31}H_{48}O_4$, as needles, m. p. 253—256·5°, undepressed in m. p. when mixed with the specimen described above.

The acid fraction was crystallised from acetone–light petroleum, to give the acid, $C_{30}H_{46}O_5$, as needles (40 mg.), $[\alpha]_D$ −37°, m. p. and mixed m. p. 272—273° (Found: C, 74·05; H, 9·6%). Light absorption: Max. at 2260 Å (ε 12,720). Esterification of the acid with diazomethane gave the methyl ester, $C_{31}H_{48}O_5$, m. p. 231—232·5°, undepressed when mixed with the specimen described above; it shows a maximum at 2250 Å (ε 15,000).

Treatment of the Methyl Ester, $C_{31}H_{48}O_5$ with Alkali.—A solution of the methyl ester (0·25 g.) in methanolic potassium hydroxide (20%; 40 c.c.) was kept in an autoclave at 200° for 8 hr. The cold mixture was diluted with water (no precipitation), the solution acidified with dilute hydrochloric acid, and the precipitated acid isolated by means of ether. The acid separated from methanol–acetone as an amorphous solid, m. p. 332—333° (decomp.), $[\alpha]_D$ −28° (*c*, 1·25 in pyridine) (Found: C, 70·8, 70·8; H, 9·6, 9·7; OMe, 4·5. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·6. $C_{30}H_{47}O_5{\cdot}OCH_3$ requires C, 71·8; H, 9·7; OMe, 6·0%). The amorphous acid does not give a colour with tetranitromethane. Light absorption: Max. at 2800 Å (ε 390).

The *dimethyl ester*, prepared from the amorphous acid by treatment with ethereal diazomethane, separated from acetone–*n*-hexane as hexagonal plates, m. p. 228°, $[\alpha]_D$ −35° (*c*, 1·0) [Found: C, 72·3; H, 10·0; OMe, 11·1. $C_{30}H_{46}O_4(OCH_3)_2$ requires C, 72·1; H, 9·8; OMe, 11·6%]. The dimethyl ester does not give a colour with tetranitromethane.

Acetylation of the dimethyl ester by treatment overnight with acetic anhydride in pyridine gave the *dimethyl ester acetate*, prisms, m. p. 202·5—203·5°, $[\alpha]_D$ −28·5° (*c*, 1·3), from *n*-hexane (Found: C, 71·0, 71·2, 70·8; H, 9·8, 9·8, 9·5. $C_{34}H_{54}O_7$ requires C, 71·0; H, 9·5%). Light absorption: Max. at 2800 Å (ε 340).

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Some Thermodynamic Properties of Compounds of the Formula MX_4. *Part II.* Tetra-alkyl Compounds.*

By L. A. K. STAVELEY, J. B. WARREN, H. P. PAGET, and D. J. DOWRICK.

[Reprint Order No. 4945.]

The melting points, heats of fusion and transition, and heat capacities from ~95° K to about 20° above the melting point have been measured for the following substances: tetramethyl-tin and -lead, tetraethylmethane (3 : 3-diethylpentane), tetraethyl-silicon, -germanium, -tin, and -lead. The observations made with the last two compounds supplement the work described in Part I* on their unusual polymorphism. Which of the numerous forms of these two substances are produced on crystallization appears to depend on factors such as the degree of purity, the nature of the surfaces of the confining vessel, and the thermal history of the sample before crystallization. Tetraethylgermanium can crystallize in two forms, but only one melting point has been recorded for each of the other four substances.

The properties of the tetramethyl and tetraethyl compounds of the Group IV elements are compared, with special reference to incidence of polymorphism, the trend of the melting points, the entropies of fusion, and the changes of heat capacity on melting.

Some experiments have been carried out with tetrapropyltin and tetrabutyltin. A value for the melting point of each has been recorded, but the liquids crystallize with such difficulty that no calorimetric work was attempted. Their crystallization (especially that of tetrabutyltin) provides an example of the so-called " memory effect," in that, although it is normally very reluctant to take place, yet it occurs much more readily if, after fusion, the temperature of the liquid is not allowed to rise more than 2—3° above the melting point before it is cooled again.

IN Part I (*loc. cit.*), the remarkable polymorphism of tetraethyl-tin and -lead was described. This polymorphism was discovered during calorimetric work on tetraethyltin, which formed part of a systematic study of the thermodynamic properties of the tetramethyl and tetraethyl compounds of Group IV elements. We report here the complete results of this study. Measurements have been made of c_p from ~95° K to about 20—30° above

* The paper by Staveley, Paget, Goalby, and Warren (*J.*, 1950, 2290) is to be regarded as Part I.

the melting point, and of heats of phase changes, for each of the seven substances enumerated in the Summary (above). Since Aston and his co-workers have already measured these quantities for tetramethylmethane (*neo*pentane) (Aston and Messerly, *J. Amer. Chem. Soc.*, 1936, **58**, 2354) and tetramethylsilicon (Aston, Kennedy, and Messerly, *ibid.*, 1941, **63**, 2343), the work described here makes possible a comparison of some of the properties of the tetramethyl and tetraethyl compounds, and supplements the earlier observations on the unusual polymorphism displayed by some of these substances. In addition, some preliminary experiments have been carried out on tetrapropyltin and tetrabutyltin. Unfortunately, these liquids crystallized so reluctantly even when stirred that it is doubtful if they would do so at all in a calorimeter of conventional design.

Experimental

The experiments on tetramethyl-tin and -lead, and some of those on tetraethyltin and tetraethylmethane were carried out in the calorimeter described by Staveley and Gupta (*Trans. Faraday Soc.*, 1949, **45**, 50), here referred to as calorimeter I. For the other measurements, the calorimeter was rebuilt to a new design. Fig. 1 shows the construction of this new calorimeter (calorimeter II). A disadvantage of calorimeter I was the liability of the platinum thermometer wound on the surface of the inner container to change its characteristics, necessitating frequent re-calibration. In calorimeter II, the temperatures at which measurements were made were determined with a previously calibrated three-junction copper–constantan thermocouple inserted in a re-entrant tube of the inner container. A copper wire (S.W.G. 48, resistance ~115 ohms at 0°) served both as a heater and as a resistance thermometer. It was calibrated *in situ* as a resistance thermometer against the thermocouple, and used to determine temperature changes in measurements of c_p. Its re-calibration could therefore be easily carried out at any time. The other main difference between calorimeters I and II was in the arrangements made for introducing the substance under investigation. In calorimeter I, this was done by condensation *via* a fixed inlet tube, an operation which was very slow with the less volatile alkyl compounds. In calorimeter II, the substance was inserted through a short filling tube, which was then closed with a cap sealed with low-melting solder. The apparatus had therefore to be dismantled and re-assembled with each change of substance. Other details of the construction of calorimeter II will be clear from Fig. 1 and the accompanying legend.

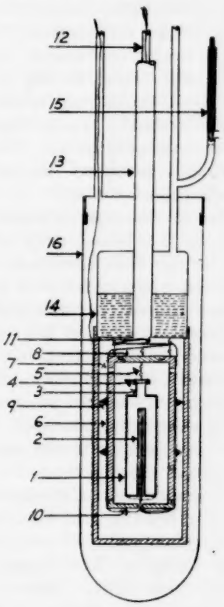

Fig. 1. *Calorimeter designated as calorimeter II.* 1, Copper inner container, wound with copper resistance thermometer-heater. 2, Three-junction thermocouple in re-entrant tube. 3, German silver filling-tube. 4, Removable cap. 5, Silk suspension. 6, Copper radiation shield. 7, Hole in shield. 8, Removable top. 9, Conical plastic plugs to centralize shield. 10, Threaded bottom of shield, with hole for electrical leads. 11, Cable of leads, which passes up the tube 12. 12, Tube for leads, situated behind the central tube. 13, Central tube for evacuation of inner compartments of calorimeter. 14, Copper vessel half-filled with lead. 15, Valve for introduction of refrigerant. 16, Chromium-plated outer brass can.

The three-junction thermocouple was calibrated (1) at the normal b. p. of oxygen, (2) at

four other temperatures against a strain-free platinum resistance thermometer of the Meyers type (*J. Res. Nat. Bur. Stand.*, 1932, **9**, 807). These temperatures were the f. p.s of carbon tetrachloride, chloroform, *n*-heptane, and carbon disulphide. To carry out the calibration at any one of these, a purified sample of the liquid, in which the platinum thermometer and thermocouple were immersed, was frozen slowly in an apparatus of the type described by Mair, Glasgow, and Rossini (*ibid.*, 1941, **26**, 591). This apparatus seems to be very suitable for calibration work of this kind. From the five pairs of temperature–E.M.F. values, a deviation curve was constructed, Scott's data for a standard thermocouple (*ibid.*, 1940, **25**, 459) being used. A smooth curve was drawn from which none of the experimental points was further removed than 0·5 μv, which at 0° corresponded to ~0·004° and at −180° to ~0·01°.

All E.M.F. measurements were carried out with a Tinsley Vernier Potentiometer, and could be made to 0·5 μv over the range 0—180,000 μv. The resistance of the copper thermometer-heater was determined at intervals of about 5° by current and voltage measurements. For convenience in converting resistance changes into temperature changes (which were estimated to 0·001°), the deviation curve method was again employed. A plot was made (to which tangents were then drawn) of the deviations of the observed resistances from those which would have been measured at the same temperatures had the resistance varied linearly between 0° and the lowest calibration temperature.

The energy input during a heating period was determined by measuring the current C through the thermometer-heater, and the voltage across it, V, and then plotting CV against time. For normal c_p measurements, this plot was linear, so that the estimation of the energy input was a simple matter. The time of heating was measured to 0·05 sec. with a stop-watch automatically switched on and off with the heating current, and calibrated against the Greenwich time signals.

The inner container of calorimeter II was the same as that of I, except that the copper vanes included in the latter were omitted from the second calorimeter. There was no marked increase in the time needed to reach thermal equilibrium. The quantity of substance under examination was usually 4—5 c.c.

With a calorimeter as small as this, the highest precision cannot be expected, since the total thermal capacity of the inner container and its contents is small, while the contribution of the inner container is relatively large. On the other hand, it is possible to make measurements on substances only available in small amounts. We do not claim a higher accuracy for our values of c_p and heats of phase changes than approximately 1%, or perhaps 0·5% in favourable cases. We consider, however, that this degree of accuracy is adequate for our main purpose in making these measurements, which is to obtain reasonably reliable thermodynamic information for groups of closely related compounds, with the object of studying the relation between physical properties and chemical constitution.

Tetramethyl-tin and -lead were prepared from stannic chloride and methylmagnesium iodide, and lead chloride and methylmagnesium chloride, respectively, as described by Krause and von Grosse ("Die Chemie der metall-organischen Verbindungen," Borntraeger, Berlin, 1937, pp. 315, 389). After removal of ether the crude tetramethyltin appeared to be contaminated with methyl iodide, from which it was freed by heating with pyridine in a sealed tube at 80° for 1½ hr. It was then twice fractionated at 0° in a column of the type described by Clusius and Riccoboni (*Z. physikal. Chem.*, 1937, *B*, **38**, 81). The impure tetramethyl-lead was likewise fractionated twice in the same column at a temperature of 10·5°.

A sample of tetraethylmethane was kindly supplied by the Anglo-Iranian Oil Co. Ltd. It had been prepared in the Dyson Perrins Laboratory, Oxford, by J. C. Smith and S. H. Morell. The quantity available was too small to permit further purification. Tetraethylsilicon was prepared from silicon tetrachloride by two methods, by reaction with ethylmagnesium bromide (Krause and von Grosse, *op. cit.*, p. 260), and also by reaction with ethyl-lithium (Gilman and Clark, *J. Amer. Chem. Soc.*, 1946, **68**, 1675). The product was purified by treatment with concentrated sulphuric acid to remove any triethylsilicon chloride, and fractionated twice. The sample of tetraethylgermanium was that referred to in Part I, but before the measurements described here were undertaken it was treated with potassium hydroxide pellets to remove hydrogen bromide, and then twice fractionated. The experiments with tetraethyltin were carried out with sample D (Part I). The tetraethyl-lead used was supplied by the Associated Ethyl Company, and further purified by a double fractionation. Some experiments were deliberately performed with a less pure sample of this substance.

Tetrapropyltin and tetrabutyltin were prepared from stannic chloride by the Grignard reaction. The *n*-propyl chloride and *n*-butyl chloride used to make the Grignard reagents had

been purified by fractionation. The ethereal solutions of the crude products were treated with ammonia to remove the trialkyltin chlorides, but only small amounts of these seemed to be present. After removal of the ether, the liquids were fractionated at ~4 mm.

Results

Melting Points.—We shall first present the additional information obtained in this work about the polymorphism in these compounds. Previously, this had been most fully investigated for tetraethyltin. In the experiments with this substance in calorimeter II three forms were obtained, namely, those which had been designated *b*, *e*, and *g* in Part I, and in contrast to the experiments of Series I, Part I, the substance now crystallized exclusively in one of these forms. In 15 crystallizations, *e* was produced ten times, *b* four times, and *g* only once. Rapid cooling seemed to favour crystallization into form *b*, whereas crystallization on warming the glass formed by slow cooling normally gave form *e*. Attempts to measure accurately the m. p. and heat of fusion of form *b* were defeated by its spontaneous passage on melting into form *e*. The m. p. of *b* was confirmed, however, as being 138·7° ± 0·1° K. The form *g* had never before been obtained in calorimetric work. A stepwise determination of its m. p. was not carried out, but from a continuous-fusion run the m. p. was estimated as 143·05° K, which agrees quite well with the value given in Part I.

These further experiments with tetraethyltin, and more particularly with tetraethyl-lead, have shown that which of the numerous forms of these substances appears on crystallization seems to be markedly affected by the purity of the sample. Thus, our most highly purified specimen of tetraethyl-lead (with 0·08 mole % of impurity), in each of 20 experiments in which the thermal treatment was varied as much as possible, crystallized in one form only, melting at 142·94° K, whereas the highest-melting form which we had hitherto obtained melted at 141·5° K. This difference prompted us to make measurements on a sample which, owing to decomposition or oxidation (or both), was much less pure (~1·2 moles % of impurity). With this, the form melting at 142·94° K was never obtained in 8 experiments. Crystallization gave four forms with the following m. p.s (after correction for the depression due to the impurity present): 136·6° ± 0·1° (once; on this occasion most of the substance crystallized in the form melting at 138·56°); 138·56° (five times); 139·3° ± 0·1° (twice); 141·5° ± 0·1° (once). (The second was accurately estimated by a stepwise determination. The other values are less accurate, as they depended on runs in which the sample was continuously heated.) The form melting at 138·56° was that most frequently observed in the work described in Part I. Combining the results of this earlier work (Part I) with those just given (II), we have the following list of m. p.s for tetraethyl-lead: *a*, 135·6° (I); *b*, 136·6° (I, II); *c*, 137·4° (I); *d*, 138·2° (I); *e*, 138·55° (I, II); *f*, 139·3° (II); *g*, 141·5° (I, II); *h*, 142·94° K (II).

The thermodynamic properties of tetramethyl-lead, tetraethyl-lead, and tetraethylmethane have been investigated independently by Dr. G. B. Guthrie, jun., at the Petroleum Experiment Station of the U.S. Bureau of Mines. We are very grateful to him for giving us details of his results before their publication. He reports finding five m. p.s for tetraethyl-lead, four of which agree within 0·1° with our values *e*, *f*, *g*, and *h*; and in addition he obtained evidence that there are forms with lower m. p.s.

In Part I, the possibility of correlating the m. p.s of the numerous forms of tetraethyltin with those of the lead compound was briefly considered. No finality can be reached even now in this matter, but the discovery of a form of the lead compound with a higher m. p. (142·94° K) suggests the following as the most likely pairing:

M. p. (Sn)	147·1°	145·8°	144·1°	143·15°	142·12°	141·87°	140·6°	139·8°	138·7°	138·1°
M. p. (Pb)	142·9	141·5	139·3	138·55° or 138·2°	137·4	—	136·6	135·6	—	—
Δ(Sn − Pb)	4·2	4·3	4·8	4·6 or 4·95	4·7	—	4·0	4·2	—	—

The preliminary experiments with tetraethylgermanium described in Part I did not show any evidence of crystallization in more than one form. The behaviour of the purer sample used in the present investigation was carefully examined. On cooling, crystallization usually occurred rapidly about 10° below the m. p., and in 22 out of 23 experiments (in which the thermal treatment was varied as much as possible), the solid produced melted at ~180·1°, the corrected m. p. being 180·47° K. In the remaining experiment, however, the liquid supercooled to 90° without crystallizing, and when the glass was warmed it crystallized into a form which melted at 183·3°. Although this experiment could not be reproduced there is no reason to doubt its validity, and it is interesting that this higher m. p. is near the only one previously recorded for this substance (183·1°; Dennis and Hance, *J. Amer. Chem. Soc.*, 1925, **47**, 370).

The following compounds crystallized in one form only: tetramethyl-tin and -lead, tetraethylsilicon, and tetraethylmethane. The experiments with the first two substances were carried out before the discovery of the polymorphism of their tetraethyl analogues, and consequently a deliberate search for more than one crystalline form was not made. Tetraethylmethane and tetraethylsilicon, in spite of many variations in thermal treatment, each always gave one and the same form. The tetramethyl compounds always crystallized very readily. With the tetraethyl compounds, the degree of supercooling before crystallization (or alternatively, the difficulty experienced in effecting crystallization) increased progressively with increasing molecular weight, probably because with the passage from the carbon to the lead compounds the molecules become less compact and so interlock more in the liquid state, with the result that the reorientation or alignment necessary for the formation and growth of crystal nuclei becomes more and more difficult.

The experiments with tetrapropyltin and tetrabutyltin were carried out with the apparatus used for the experiments of Series III, Part I, so that crystallization could be assisted by stirring, since all attempts to crystallize tetrapropyltin in glass vessels without stirring had failed. Even with stirring, these two liquids were very reluctant to crystallize, tetrapropyltin particularly so. Attempts to freeze small samples (of different degrees of purity) with which to inoculate the main bulk were unsuccessful, and the addition of powdered glass had no effect. Below about 140° K for tetrapropyltin, and 158° K for tetrabutyltin, the supercooled liquids were too viscous for the stirrer to operate.

It was established without doubt that tetrapropyltin has an m. p. at 163·9° ± 0·1° K, and tetrabutyltin one at 176·1° ± 0·05° K. These values were derived from temperature–time curves during fusion, but it was not possible to follow these curves for sufficiently long to permit the estimation from them of the impurity content of the samples, and so to correct the observed m. p.s for the depression due to the impurities. It appeared, however, that the samples were of satisfactory purity, and that these corrections would be small.

There was some indication in two runs with tetrapropyltin that another form was present of m. p. a few tenths of a degree above that just quoted, but we were unable to obtain more definite information.

Although these liquids ordinarily crystallized with great difficulty, it was found (especially with tetrabutyltin) that crystallization took place much more readily if, after the fusion of the crystals, the temperature was not allowed to rise more than 2—3° above the m. p. before the liquid was cooled again. This effect, sometimes known as the "memory" effect, has been observed and studied for other liquids, *e.g.*, by Richards for salol and benzophenone (*J. Amer. Chem. Soc.*, 1932, **54**, 179) and by Turnbull for gallium (*J. Chem. Phys.*, 1950, **18**, 198). The effect is probably due to the persistence of crystal nuclei just above the m. p. in cavities in the walls of the containing vessel or in the surfaces of heterogeneous impurities. If a liquid can crystallize in more than one form, therefore, it might be expected that the crystal nuclei would induce crystallization back into the modification of which they are the residue, so to speak, so the effect is of doubtful value in a search for other crystalline forms.

Transitions in Tetraethylmethane.—Within the temperature range from ~95° K to the m. p., the only substance found to have transitions was tetraethylmethane. In our first experiments on this compound it appeared to possess one transition at about 210° K, taking place over a range of about 1° and attended by considerable superheating and supercooling, and having a heat of transition of ~300 cal./mole. We were then privately informed by Dr. G. B. Guthrie that he had discovered two transitions, at 208·4° and 210·4° K. On carefully re-examining the behaviour of the crystals in this region, we also observed two transitions, for which transition temperatures of 208·8° ± 0·2° and 210·1° ± 0·2° K were recorded. These were the temperatures at which the rates of increase of temperature with time were a minimum during runs in which the crystals were heated continuously, though very slowly, through the transition region. (As there was considerable supercooling, each such run was preceded by repeated variation of the temperature between ~170° and that of the lower transition. Even so, in several such runs there was no evidence of any transition, so that the solid must have remained throughout in the high-temperature form.) Two such runs showed arrests at 210·1—210·2° only. In two further runs, however, there were arrests at ~208·8° (preceded by slight superheating) followed by very small arrests at 210°, the amount of heat absorbed at this higher temperature being undoubtedly much less than in the first two runs. If we denote the form stable from 210° to the m. p. as I, that stable from 208·8° to 210° as II, and that stable below 208·8° as III, these observations would appear to mean that sometimes in the heating run it was supercooled II which was being heated, but that sometimes after III had changed into II this did *not* then

change completely into I at 210°. This seems curious, particularly in view of the fact that reproducible values were obtained for the heat of fusion and m. p., showing that it was always form I which was melted. We do not fully understand our observations on the transitions in this compound, which seem to merit more detailed investigation.

TABLE 1. *Combined heat of the transitions in tetraethylmethane, $\Delta H_{tr.}$, in cal./mole*
(Throughout this paper, the calorie is the thermochemical calorie, *i.e.*, 4·184 absolute joules.)

Mass of sample (g.)	Calori-meter	Temp. interval (°K)	$\Delta H_{tr.}$	Mass of sample (g.)	Calori-meter	Temp. interval (°K)	$\Delta H_{tr.}$
3·694	I	207·43—214·33°	319	3·289	II	206·20—215·71	322·2
,,	I	206·98—216·00	302·5	,,	II	203·70—213·49	290·7
,,	I	206·95—216·52	296·5			Mean value	304
,,	I	206·72—216·55	292				

No attempt was made to determine the separate heats of each transition, but a number of measurements were made of the extra heat absorbed in heating through the transition region, after the sample had been subjected to the thermal treatment mentioned above. The results are presented in Table 1, and show that the combined heats of transition amount to 304 cal./mole.

Melting Points and Degrees of Purity of Samples Used.—To assess the purity of the samples used, m. p.s were determined by the usual procedure of melting the solid in stages and measuring the steady temperature reached at the end of each stage. If these temperatures are plotted against $1/F$ (F = fraction melted), a straight line should be obtained if the impurities are liquid-soluble and solid-insoluble and if the solution of them in the major component obeys Raoult's law. Extrapolation of the line to $1/F = 0$ gives the m. p. (T_m) of the pure compound. By using measured values of the latent heat of fusion, the impurity content of the actual sample can be determined. The results are given in Table 2. Some plots of T against $1/F$ do not

TABLE 2. *Melting points and degrees of purity of samples used.* (T_m is the extrapolated m. p. for a 100% pure sample. The calculated impurity content, x, is given as moles %.)

$SnMe_4$	% melted	16·5	32·7	50·0	67·7	}	$T_m = 218·18°$; $x = 0·26$
	T	217·47°	217·81°	217·97°	218·08°		
$PbMe_4$	% melted	21·6	42·3	63·0	83·8	}	$T_m = 242·92°$; $x = 0·24$
	T	242·253°	242·558°	242·646°	242·716°		
CEt_4	% melted	20	40	60	80	}	$T_m = 240·13°$; $x = 0·50$
	T	239·21°	239·61°	239·75°	239·84°		
$SiEt_4$	% melted	21·7	43·4	65·1	86·8	}	$T_m = 189·36°$; $x = 0·10$
	T	189·30°	189·31°	189·32°	189·34°		
$GeEt_4$	% melted	20	33	48	59	74·5	90
	T	180·28°	180·35°	180·415°	180·428°	180·438°	180·442°
		$T_m = 180·47°$; $x = 0·11$.					
$SnEt_4$	% melted	22·2	38·7	54·8	71·0	}	$T_m = 142·15°$; $x = 0·08$
	T	142·00°	142·12°	142·13°	142·135°		
$PbEt_4$ [a]	% melted	20	40	60	80	}	$T_m = 142·94°$; $x = 0·08$
	T	142·85°	142·87°	142·88°	142·90°		
$PbEt_4$ [b] ...	% melted	20	40	60	80	}	$T_m = 138·56°$; $x = 1·2$
	T	136·56°	137·51°	137·89°	138·02°		

[a] Purest sample used. [b] Impure sample which had crystallized in a form of lower m. p.

give good straight lines if all the points are given equal weight: for these, more importance has been attached to the points for the later stages of melting.

The values in Table 2 for tetraethyl-germanium, -tin, and -lead refer to that form of each substance which was most frequently formed. In addition, for the lead compound results are given for the less pure sample referred to above in connection with the polymorphism of this substance.

For tetramethyl-lead, Grüttner and Krause (*Annalen*, 1918, **415**, 338) gave −27·5° c as the m. p., which is 2·7° higher than our figure. For tetraethylmethane, the most recent value in the literature is −33·110° ± 0·005° (Streiff *et al.*, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 53), which is 0·08° lower than our value.

FIG. 2.

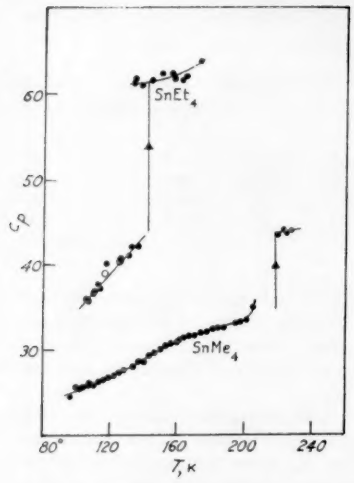

FIG. 3.

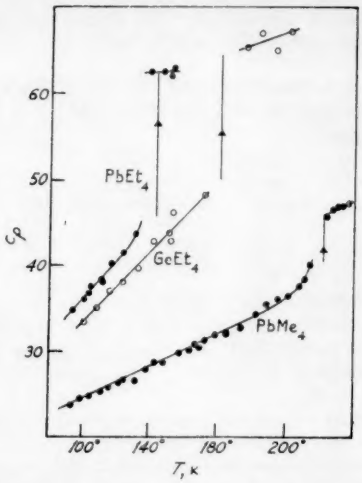

FIG. 2. *Plot of experimental values of* c_p, *in cal./mole/°, against temperature in* °K *for tetramethyltin and tetraethyltin.* The vertical lines in this figure and in Figs. 3 and 4 indicate the m. p. of that form of the compound to which c_p refers, and the length of these lines represents the increment in c_p on melting. The full circles for tetraethyltin refer for the solid to the form of m. p. 142·15° K, and the two open circles refer to the solid form of m. p. 138·5° K.

FIG. 3. c_p *plotted against* T (*in* °K) *for tetramethyl-lead* (*full circles*), *tetraethylgermanium* (*open circles*), *and tetraethyl-lead* (*full circles*).

FIG. 4.

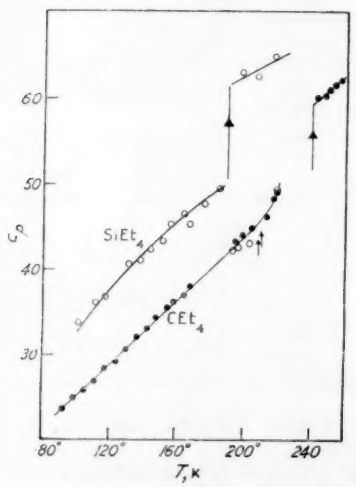

FIG. 5.

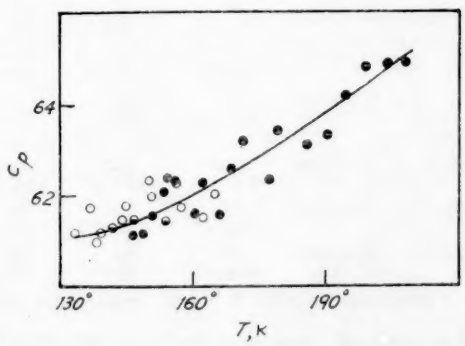

FIG. 4. c_p *plotted against* T (*in* °K) *for tetraethylsilicon* (*open circles*) *and tetraethylmethane* (*full circles, calorimeter I; open circles, calorimeter II*). The small arrows near the lower curve show the temperature of the transitions in tetraethylmethane.

FIG. 5. c_p *for liquid tetraethyltin plotted against temperature in* °K. Open circles, uncrystallized liquid (*i.e.*, the sample was cooled from room temperature to a few degrees below the m. p. without crystallization occurring and the c_p measurements were then made). Full circles, liquid obtained on melting form of m. p. 142·15°. Half-shaded circles, liquid produced on melting form of m. p. 138·5°.

TABLE 3. *Values of* c_p *(in cal./mole/degree) at regular temperature intervals, taken from smoothed curves through the experimental points after these had been corrected, where necessary, for premelting.* (The horizontal line in each column separates the results for crystal and liquid. Tetramethyl-tin and -lead were studied in calorimeter I, tetraethylmethane in calorimeters I and II, and the remaining substances in calorimeter II. The figures for crystalline tetraethyl-germanium, -tin, and -lead refer to the forms of m. p. 180·47°, 142·15°, and 142·94° K, respectively.)

T (°K)	$SnMe_4$	$PbMe_4$	CEt_4	$SiEt_4$	$GeEt_4$	$SnEt_4$	$PbEt_4$
90	—	—	23·2	—	—	—	33·65
100	25·3	24·2	24·95	32·4	33·2	—	36·0
110	26·05	25·15	26·75	35·1	35·3	36·75	38·4
120	26·85	26·05	28·65	37·55	37·4	39·05	40·75
130	27·75	27·0	30·55	39·7	39·5	41·3	43·1
140	28·8	27·95	32·6	41·65	41·6	42·6 [b]	62·5 [a]
150	30·05	28·9	34·6	43·5	43·7	61·55	62·5
160	31·0	29·85	36·4	45·2	45·8	62·0	—
170	31·7	30·8	38·2	46·8	47·9	62·45	—
180	32·1	31·75	40·0	48·15	—	63·0	—
190	32·45	32·75	41·75	61·5	64·8	63·7	—
200	32·65	33·8	43·3	62·5	65·5	64·45	—
210	32·7	34·7	45·5 [c]	63·6	66·3	65·3	—
220	43·7	35·45	47·5 [c]	64·6	67·0	—	—
230	44·2	36·4	49·5 [c]	—	—	—	—
240	—	—	59·5 [a]	—	—	—	—
250	—	46·65	60·95	—	—	—	—
260	—	47·7	62·35	—	—	—	—

[a] Supercooled liquid. [b] Extrapolated. [c] Form stable above transition temperatures.

Heat Capacities.—These are plotted against temperature in Figs. 2, 3, and 4. Values at regular temperature intervals, obtained from smoothed curves after correction for premelting, are given in Table 3. For tetraethyl-tin and -lead, some measurements were made on the supercooled liquids. The results for crystalline tetraethyltin refer to the form melting at 142·15° K. Two c_p measurements on the form melting at 138·5° K were made, and within experimental error the values obtained were the same as for the form of m. p. 142·15° K.

In view of certain claims that, owing to some kind of rotational isomerism, certain liquids show a variable c_p depending on their thermal history, a careful examination of the heat capacity of liquid tetraethyltin in the neighbourhood of the m. p. was made; c_p was measured on liquid cooled from room temperature to about 130° K (without freezing), and on liquid produced by melting the crystals of m. p.s 138·5° and 142·15° K. The results are plotted in Fig. 5. As is usual, the c_p points for a liquid show a rather larger scatter than for a solid, but within experimental error there is no indication that c_p for the liquid varies according to its thermal history. This is to be expected, since (as pointed out in Part I) the constancy of the m. p.s of the different forms implies that any equilibrium in the liquid is established relatively quickly at these temperatures.

Heat of Fusion.—The results are given in Table 4.

TABLE 4. *Heats of fusion,* ΔH_f, *in cal./mole.* (For the polymorphic substances, the figures refer to the same forms as the results in Table 3.)

Substance	Mass of sample (g.)	Temp. interval	ΔH_f	Mean	Substance	Mass of sample (g.)	Temp. interval	ΔH_f	Mean
$SnMe_4$	5·323 *	191·77—222·16°	2251	2256	$SiEt_4$	3·856 †	182·50—193·11°	3116	3110
		196·81—223·32	2268				186·04—197·61	3115	
		195·04—222·23	2238				184·52—194·29	3098	
$PbMe_4$	8·158 *	220·16—249·41	2585	2581	$GeEt_4$	5·051 †	176·72—191·64	2960	2965
		222·97—251·68	2577				172·62—190·53	2971	
		220·58—249·90	2580				175·09—191·22	2963	
CEt_4	3·694 *	226·09—244·55	2409	2398	$SnEt_4$	5·8695 †	135·05—147·06	2191	2186
		226·08—244·57	2397				138·09—145·00	2203	
		225·04—244·99	2394				136·91—145·84	2179	
	3·289 †	231·50—245·19	2397				138·77—146·20	2170	
		225·96—243·58	2399		$PbEt_4$	8·758 †	133·90—151·05	2108	2101
		227·41—245·56	2392				135·30—150·91	2095	

* Calorimeter I. † Calorimeter II.

Discussion

In Part I, the opinion was expressed that the ability to crystallize in numerous solid forms, so far as the tetramethyl and tetraethyl compounds are concerned, is probably confined to tetraethyl-tin and -lead, and it was suggested that the phenomenon arises because the molecules of these two substances exhibit in the solid state a form of rotational isomerism. The reasons given in Part I for this opinion still hold, and the views expressed there are not changed by the new facts presented in this paper, but at the same time it will now be clear that it is unwise to conclude that a substance of this kind cannot exist in more than one form simply because the same sample in the same apparatus always crystallizes in the same form, even in as many as twenty experiments. Thus, the polymorphism of tetraethyl-lead would never have been suspected from our own calorimetric experiments with the purer sample, while the fact that tetraethylgermanium in just one experiment out of 23 crystallized in a different form may mean that there are other undiscovered solid forms of this compound. Another illustration of the capricious nature of the crystallization process is the observation that in the earlier calorimetric work with tetraethyltin (Series I of Part I), two or three forms were sometimes produced simultaneously when the supercooled liquid crystallized, and in a continuous-fusion experiment these melted in turn without those of lower melting point changing into those of higher melting point. In the work reported here, only one form was produced on crystallization, and when this was that of m. p. 138·5° it tended to recrystallize into the form of m. p. 142·15° K. Presumably the crystallization process is strongly influenced by impurities, both heterogeneous and (in view of the results with tetraethyl-lead) homogeneous as well, and also perhaps by the nature of the walls of the containing vessel. In addition, the thermal treatment has an effect, as already pointed out.

Table 5. *Melting points* (T_m) *and entropies of fusion* (ΔS_f, *in cal./mole/°*) *of compounds of formula* MX_4.

X =	Cl		Me		Et	
M	T_m	ΔS_f	T_m	ΔS_f	T_m	ΔS_f
C	250·23°	7·10 [a]	256·53°	7·42 [a]	240·13°	11·43 [a]
Si	205·5	9·08	174·12	9·465	189·36	16·42
Ge	233·6	—	185	—	180·47 [b]	16·43
Sn	239·9	9·11	218·18	10·34	142·15 [b]	15·38
Pb	~258	—	242·92	10·62	142·94 [b]	14·70

[a] Combined entropies of fusion and transition. [b] Melting points of forms for which ΔH_f was measured. Figures for CMe_4 from Aston and Messserly, *loc. cit.*; for $SiMe_4$ from Aston, Kennedy, and Messerly, *loc. cit.*; for the tetrachlorides, from Hildebrand and Scott, "The Solubility of Non-electrolytes," Reinhold Publishing Corpn., New York, 1950, p. 59.

In Table 5, the entropies of fusion ΔS_f and melting points T_m of the tetraethyl and tetramethyl compounds are presented, together with data for the tetrachlorides. T_m is abnormally high for the carbon compounds, as pointed out and commented on in Part I. In the tetrachlorides and tetramethyl compounds, T_m rises from silicon to lead, and ΔS_f is almost constant or slowly increases. This is not so for the tetraethyl derivatives, where there is considerable drop in T_m on going from germanium to tin and a decrease in ΔS_f. The tetraethyl series may not be the only one in which some rather sudden change of this kind occurs. The continuous fall in melting point found in this series is also encountered in the tetrabenzyl compounds (at least as far as the tin compound—the melting point of tetrabenzyl-lead has not been measured), and it is noteworthy that the tetrabenzyl molecules have the same sort of shape as those of the tetraethyl compounds. (There is no such steady or pronounced downward trend in melting point in the tetraphenyl and tetra-*p*-tolyl series.) Also, the value of 163·9° K recorded above for the melting point of tetrapropyltin is considerably lower than the value 200° K for tetrapropylgermanium given by Tabern, Orndorff, and Dennis (*J. Amer. Chem. Soc.*, 1925, **47**, 309), the difference being about the same as that between the melting points of tetraethyl-germanium and -tin.

For the tetramethyl compounds the values of ΔS_f are somewhat greater than for the chlorides, and they rise with increasing size of the central atom. A possible reason for this may be the following. The potential barrier restricting rotation of the methyl groups decreases rapidly as the radius of the central atom increases, and for the tin and lead compounds the rotation is probably relatively free for molecules in the gaseous state (French and Rasmussen, *J. Chem. Phys.*, 1946, **14**, 389). In the condensed states, molecular interlocking may to some extent interfere with this internal rotation, especially in the solid state. When the crystal melts, the increase in volume should permit a greater degree of rotational freedom of the methyl groups, but the more compact molecules will have less to gain in this way, and the corresponding contribution to the entropy change will therefore increase on going from carbon to lead.

Larger values of ΔS_f for the tetraethyl compounds are, of course, to be expected. It will be noticed that the trend in ΔS_f has now disappeared. It would be interesting to have values for the different forms of the tin and lead compounds: if the "pairing" for these forms suggested on p. 1995 is correct, then the values given in Table 5 for tetraethyl-tin and -lead are not strictly comparable.

It is significant that the increments in c_p on melting are quite large for the tetraethyl compounds (C, 8; Si, 11·5; Ge, 14; Sn, 18; Pb, 16·5 cal./mole). The corresponding increments for the tetramethyl compounds are much smaller (C, 5; Si, 5; Sn, 9·5; Pb, 8 cal./mole). Admittedly, if c_v values were available the increments in c_v would no doubt be less, since $(c_p - c_v)$ is generally greater for liquids than solids. However, $(c_p - c_v)$ for liquids does not usually much exceed 10 cal./mole and may be less than this, while for the solid near the melting point it probably amounts to several cal./mole. Hence there is probably a considerable increase in c_v on melting, particularly for tetraethyl-germanium, -tin, and -lead. Part of this increase may well arise from the fact that for substances such as these which are liquid over a large range of temperature, there can be a considerable so-called configurational contribution to the heat capacity near the melting point (cf. Staveley, Hart, and Tupman, *Discuss. Faraday Soc.*, 1953, **15**, 130). Since the tin and lead compounds, while having the highest boiling points, have the lowest melting points, this configurational contribution at the melting point would be larger for them than for the other tetraethyl compounds. But it is also possible that some of the increase in heat capacity on melting may arise from the intramolecular degrees of freedom. Usually it is supposed (and for small molecules it is undoubtedly a good approximation) that the intramolecular contribution to the heat capacity of a substance depends only on the temperature and not on the physical state of the substance. But it is possible for molecules like those of the tetraethyl compounds, which are not only fairly complex but are also, as it were, potentially flexible molecules which must interlock somewhat in the condensed states, that on passing from the solid to the more expanded liquid there is a sufficient alteration in the frequencies of some of the internal vibrations to change appreciably the corresponding contribution to the heat capacity. It would be very interesting to make a comparative study of the vibrational frequencies of these tetraethyl molecules in the gaseous, liquid, and solid states, and also of the molecules of tetraethyl-tin and -lead in the different crystalline forms.

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Alcoholates of Thorium Tetrachloride.

By D. C. Bradley, M. A. Saad, and W. Wardlaw.

[Reprint Order No. 5052.]

The reactions of thorium tetrachloride with methyl, ethyl, *iso*propyl, *n*-butyl, and *tert.*-amyl alcohol and ethylene glycol have been studied. The results are discussed in terms of the theories previously advanced to account for the reactions of other Group IVA chlorides with alcohols.

It is well established that thorium tetrachloride reacts with ethyl alcohol to give $ThCl_4,4EtOH$, in marked contrast to the behaviour of the other Group IVA tetrachlorides. So far, the behaviour of other alcohols with thorium chloride has not been studied, and it appeared that such an investigation would yield results of special significance.

With methyl, ethyl, or *iso*propyl alcohols the products conformed to the general composition $ThCl_4,4ROH$ in which thorium shows a covalency of 8; the alcoholates should therefore behave as monomeric substances in solution. The molecular weight of the tetra(*iso*propyl alcoholate) was determined in boiling *iso*propyl alcohol; the apparent molecular complexity was less than unity. This result can best be explained in terms of an ionisation equilibrium, which suggestion received support from preliminary experiments that indicated a small but significant electrical conductance of $ThCl_4,4Pr^iOH$ in *iso*propyl alcohol. This behaviour is being further investigated.

In view of the apparent 8-co-ordination of thorium in these alcoholates we examined the behaviour of the dihydric alcohol, ethylene glycol. If the glycol molecule behaved as a " chelating " agent a substance with the formula $ThCl_4,2[C_2H_4(OH)_2]$ would be expected. When the *iso*propyl alcoholate was treated with an excess of ethylene glycol in boiling benzene, reaction was not confined to the alcohol interchange since some replacement of chlorine also occurred and the product had the ratio Cl : Th = 3·38. Although this substance could not be purified, analysis demonstrated that it was not the simple derivative $ThCl_4,2[C_2H_4(OH)_2]$.

Anhydrous thorium chloride is much more difficult to prepare than the hydrated compound and we tried to use the latter as a starting material for the preparation of the alcoholates. Hecht (*Z. anorg. Chem.*, 1947, **254**, 37) has shown that certain metal chloride hydrates can be dehydrated with thionyl chloride or carbonyl chloride. We found that thionyl chloride effectively dehydrated hydrated thorium chloride and provided a product which, although not pure, was anhydrous: $ThCl_4,nH_2O + nSOCl_2 \longrightarrow ThCl_4 + nSO_2 + 2nHCl$. The impurity appeared to be a little thionyl chloride, which was retained even at 120°/0·1 mm. However, this anhydrous tetrachloride was successfully used to prepare the alcoholates since the occluded thionyl chloride reacted readily with the alcohol to give volatile products. The possibility of preparing the alcoholates directly from the hydrated tetrachloride was also explored and both ethyl and *iso*propyl alcoholates were prepared by azeotropic dehydration, benzene being used with the appropriate alcohol.

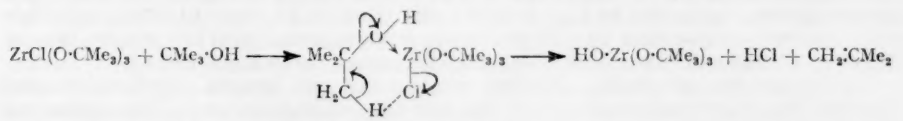
An interesting feature of the tetrachlorides of Group IVA elements is their reaction with tertiary alcohols. Anhydrous thorium tetrachloride reacted vigorously with *tert.*-amyl alcohol to produce a thorium oxychloride. Further, when the tetra(*iso*propyl alcoholate) was treated with *tert.*-amyl alcohol in benzene a rapid evolution of olefin and alkyl chloride took place. On the other hand, when the *iso*propyl alcoholate was treated with *n*-butyl alcohol in boiling benzene the main reaction was alcohol-interchange, together with some substitution of chlorine. By crystallising the product from benzene, the new alcoholate $ThCl_4,4(Bu^nOH)$ was obtained. Similarly the ethyl alcoholate was quantitatively converted into the *iso*propyl alcoholate by alcohol-interchange.

It is now clear that although the tetrachlorides of silicon, titanium, zirconium, and thorium show a well-defined variation in reactivity towards certain alcohols (ROH; where R = Me, Et, Pr^i, or Bu^n) their reactivity towards the tertiary alcohols follows a uniform

pattern. The following equations illustrate the remarkable variation of reactivity with the first type of alcohol:

$$SiCl_4 + 4ROH \longrightarrow Si(OR)_4 + 4HCl$$
$$TiCl_4 + 3ROH \longrightarrow \tfrac{1}{2}TiCl_2(OR)_2,ROH + 2HCl$$
$$2ZrCl_4 + 5ROH \longrightarrow ZrCl_3(OR),ROH + ZrCl_2(OR)_2,ROH + 3HCl$$
$$ThCl_4 + 4ROH \longrightarrow ThCl_4,4ROH$$

In this discussion, " reactivity " means the extent of the replacement of chlorine and not the reaction velocities which are indistinguishably rapid. Bradley, Halim, and Wardlaw (*J.*, 1950, 3451) suggested that the mechanisms of these reactions involved the initial co-ordination step, $R\text{–}\overset{\delta-}{O}H \longrightarrow \overset{\delta+}{M}Cl_4$, followed by an electronic rearrangement and expulsion of chloride and hydrogen ions. The reactivities were then related to a hypothetical reactivity function, $R_M = \delta+/r_M^4$, where $\delta+$ is the fractional positive charge induced on the central atom by the electron-attracting chlorine atoms and r_M is the radius of the central atom. With regard to the reactions of tertiary alcohols or other alcohols containing strongly electron-releasing alkyl groups it was later suggested (Bradley and Wardlaw, *J.*, 1951, 280) that secondary reactions involving the alcohol and hydrogen chloride liberated in the primary step, $ROH + MCl_4 \longrightarrow (RO)MCl_3 + HCl$, resulted in the formation of alkyl chloride and water. This view is supported by the occurrence of simple replacement reactions (with $SiCl_4$ or $TiCl_4$) in the presence of pyridine which stops the secondary reaction. Further when pyridinium hexachlorozirconate, which does not react with alcohols, is treated with *tert.*-butyl alcohol and ammonia in the presence of pyridine, no side reaction occurs and $ZrCl(OBu^t)_2,2C_5H_5N$ is formed (Bradley, Halim, Sadek, and Wardlaw, *J.*, 1952, 2032). Moreover, it was shown (Bradley, Halim, Mehrotra, and Wardlaw, *J.*, 1952, 4960) that when zirconium chloride *iso*propoxides react with tertiary alcohols the simple replacement (alcohol-interchange) reactions occur primarily, but in the presence of excess of tertiary alcohol a secondary reaction involving the formation of alkyl chloride and water also takes place. For the monochloride $ZrCl(O{\cdot}CMe_3)_3$, which is " non-reactive " insofar as no primary replacement of chlorine occurs, the following tentative mechanism for the formation of secondary products was proposed:



This mechanism should be applicable to chlorides of other Group IVA elements because the initial co-ordination of the tertiary alcohol to the central atom is always possible whilst the subsequent electronic rearrangement should be largely independent of the central atom. Therefore, the reaction of thorium tetrachloride with tertiary alcohols would be expected to follow a similar mechanism, especially as this tetrachloride is also " non-reactive " towards methyl, ethyl, and *iso*propyl alcohols. The alternative mechanism, $ThCl_4,4ROH \longrightarrow R^+ + [ThCl_4(OH),3ROH]^-$ involving the formation of the carbonium ion, is less likely for thorium compounds than for zirconium compounds because of the greater electropositive nature of thorium. The further possibility remains that tertiary alcohols are more reactive than other types of alcohol and cause a primary substitution reaction, $R^tOH + ThCl_4 \longrightarrow (R^tO{\cdot}ThCl_3 + HCl)$, with the thorium tetrachloride. The secondary reaction would then be the combination of hydrogen chloride and the tertiary alcohol. The greater reactivity of tertiary alcohols would be due to the increased electron density on the oxygen atom attached to the electron-releasing tertiary alkyl group.

The action of heat on $ThCl_4,4EtOH$ was also studied. The compound was heated at 100°/0·7 mm. until chloride was first detected among the volatile products. The composition of the thorium compound then approximated to $ThCl_4,2EtOH$. This was further heated under the same conditions until evolution of hydrogen chloride ceased.

From the analysis of the thorium compound it was inferred that much of the tetrachloride had been converted into thorium trichloride monoethoxide. Further heating at 170° caused decomposition, leaving an oxychloride of thorium. It appears that the alcohol in $ThCl_4$,2EtOH (involving 6-covalent thorium) is more strongly bound than in $ThCl_4$,4EtOH and this difference can be attributed to both steric and electronic effects. On steric grounds the addition of four molecules of ethyl alcohol should be less favoured than the addition of two. Moreover, in terms of electrostatic attraction between thorium and co-ordinated oxygen the combination of each additional addendum should diminish the induced positive charge on the thorium and lower the energy of co-ordination in line with the theory previously proposed (Bradley, Halim, and Wardlaw, *loc. cit.*) to explain the reactivities of Group IVA tetrachlorides with alcohol.

Experimental

All-glass apparatus was used and special precautions were taken to exclude moisture. The alcohols were dried and the analyses were carried out as previously described (Bradley, Saad, and Wardlaw, *J.*, 1954, 1091).

Hydrated Thorium Chloride.—Commercial hydrated thorium chloride (42·8 g.; Found: Th, 44·2; Cl, 24·3%; Cl : Th, 3·6) was dissolved in hydrochloric acid (*d* 1·18; 43 c.c.). During 15 days in a desiccator (H_2SO_4; *d* 1·84) the solution deposited a crystalline mass. After filtration and washing with hydrochloric acid (*d* 1·18) the crystals (36 g.) were dried for 2 days over sulphuric acid (*d* 1·84) (Found: Th, 42·0; Cl, 25·8. Calc. for $ThCl_4$,10H_2O: Th, 41·9; Cl, 25·6%).

Thionyl Chloride.—Technical thionyl chloride was purified by a method due to Dr. W. Rigby involving distillation first with turpentine oil (6% w/v) and then with linseed oil (1% w/v). The final water-white distillate gave no colour when heated with thorium chloride.

Dehydration of Thorium Chloride Hydrate.—(*a*) *With thionyl chloride.* Thionyl chloride (60 c.c.) was added to powdered thorium chloride hydrate (12·3 g.), and a rapid evolution of sulphur dioxide and hydrogen chloride occurred although the reactants became cool. After the reaction had subsided the system was boiled for 10 hr.; no more gaseous products could then be detected. The solid was filtered off, and gave a powder (10 g.) when dried at 60° under reduced pressure (Found: Th, 56·1; Cl, 38·2%; Cl : Th, 4·45). The solid, which smelled of thionyl chloride, was heated for 2 hr. at 90°/0·1 mm. (Found: Th, 56·5; Cl, 37·4%; Cl : Th = 4·34). In another experiment the solid *product* was dried for several hr. at 120°/0·1 mm. (Found: Th, 58·2; Cl, 39·1; Cl : Th = 4·39. $SOCl_2$,5$ThCl_4$ requires Th, 58·3; Cl, 39·2%).

(*b*) *By azeotropic distillation.* (i) With ethyl alcohol and benzene. Hydrated thorium chloride (13 g.) was dissolved in ethyl alcohol (400 c.c.)–benzene (400 c.c.). The solution was azeotropically distilled, a fractionating column (60 cm.; packed with Fenske helices) fitted to a Dean and Stark type of stillhead being used. Most of the water was removed as the lower layer of the ternary azeotrope of water–benzene–ethyl alcohol (10·1 c.c.) but distillation was continued until the volume of the solution had been reduced to *ca.* 250 c.c. More benzene (300 c.c.) was added and the solution concentrated by boiling until crystals appeared. Next morning the crystals (13 g.) were dried at room temperature under reduced pressure (Found: Th, 41·6; Cl, 25·6; EtO, 31·3. Calc. for $ThCl_4$,4EtOH: Th, 41·6; Cl, 25·4; EtO, 32·3%).

(ii) With *iso*propyl alcohol and benzene. Benzene (280 g.) and *iso*propyl alcohol (250 g.) were added to hydrated thorium chloride (16 g.), and the mixture azeotropically dried as in the previous experiment. In the later stages some chloride was detected in the neutral distillate. The solution was concentrated to 300 c.c. and allowed to crystallise. The crystals (17 g.) were dried at room temperature under reduced pressure. Analysis confirmed that some replacement of chloride had occurred (Found: Th, 38·1; Cl, 22·3; Pr^iO, 38·3; H_2O, 0·053%; Cl : Th, 3·86). Recrystallisation of the foregoing product from *iso*propyl alcohol gave the pure *alcoholate* (Found: Th, 37·9; Cl, 22·9; Pr^iO, 38·3. $ThCl_4$,4Pr^iOH requires Th, 37·8; Cl, 23·1; Pr^iO, 38·5%).

Reactions of Thorium Tetrachloride with Alcohols.—(1) *With methyl alcohol.* Methyl alcohol (100 c.c.) and anhydrous thorium tetrachloride (8·9 g.) reacted vigorously. The cool solution was filtered and the filtrate evaporated to dryness at 30°/0·5 mm. The solid *alcoholate* (13·8 g.) could not be crystallised from benzene, carbon tetrachloride, or light petroleum (Found: Th, 46·0; Cl, 27·7. $ThCl_4$,4MeOH requires Th, 46·2; Cl, 28·3%).

(2) *With ethyl alcohol.* Thorium tetrachloride (7·6 g.) was dissolved in ethyl alcohol (29 g.) and the filtered solution evaporated to dryness at 60° under reduced pressure. Analysis of the solid product showed that some of the addended alcohol had dissociated during drying (Found: Th, 43·4; Cl,2 6·3; EtO, 28·2%; Cl : Th, 3·96; EtO : Th, 3·34). The thermal decomposition of the alcoholate was then examined at 100°/0·7 mm. Heating was continued until the presence of chloride in the volatile products was indicated. Analysis showed that the composition of the *product* was close to $ThCl_4$,2EtOH (Found: Th, 50·3; Cl, 30·3; EtO, 18·9; Cl : Th, 3·93; EtO : Th, 1·93. $ThCl_4$,2EtOH requires Th, 49·5; Cl, 30·5; EtO, 19·3%).

This product was heated at 90—100°/0·7 mm. until evolution of chloride ceased. The analysis suggested that the solid product was a mixture of thorium tetrachloride and trichloride monoethoxide (Found: Th, 52·8; Cl, 29·2; EtO, 17·4%; Cl : Th, 3·62; EtO : Th, 1·70. Calc. for $ThCl_{3\cdot62}(OEt)_{0\cdot38}$,1·32EtOH: Th, 52·9; Cl, 29·3; EtO, 17·4%).

In another experiment the tetra(ethyl alcoholate) was heated for 2 hr. at 170°/0·1 mm. Analysis of the resulting yellow powder confirmed decomposition to an oxychloride of thorium (Found: Th, 67·1; Cl, 26·4; EtO, 2·7%; Cl : Th, 2·58; EtO : Th, 0·2).

(3) *With* iso*propyl alcohol.* Thorium tetrachloride (15 g.) was refluxed with *iso*propyl alcohol (300 c.c.) and the solution allowed to crystallise. After filtration the crystals (19 g.) were dried at room temperature under reduced pressure. The apparent molecular weight of the *tetra-alcoholate* was determined in boiling *iso*propyl alcohol in the concentration range 0·015—0·05M (Found: Th, 38·0; Cl, 23·1; Pr^iO, 38·6%; *M*, 484. $ThCl_4$,4Pr^iOH requires Th, 37·8; Cl, 23·1; Pr^iO, 38·5%; *M*, 614).

(4) *With 2-methylbutan-2-ol.* Thorium tetrachloride (7 g.) reacted vigorously with *tert.*-amyl alcohol (11 g.) but did not dissolve. The solid was filtered off and dried at room temperature under reduced pressure. Analysis confirmed that decomposition had occurred (Found: Th, 51·5; Cl, 13·6%; Cl : Th, 1·76).

Alcohol Interchange Experiments.—(1) *Action of* iso*propyl alcohol on the tetra(ethyl alcoholate).* The tetra(ethyl alcoholate) (5·8 g.) was dissolved in boiling *iso*propyl alcohol (250 c.c.), and the solution allowed to crystallise. After filtration the crystalline *tetra*(iso*propyl alcoholate*) (5·6 g.) was dried at room temperature under reduced pressure (Found: Th, 37·8; Cl, 23·0; Pr^iO, 39·1. $ThCl_4$,4Pr^iOH requires Th, 37·8; Cl, 32·1; Pr^iO, 38·5%).

(2) *Action of* n*-butyl alcohol on the tetra*(iso*propyl alcoholate*). The tetra(*iso*propyl alcoholate) (5·2 g.), benzene (64 g.), and *n*-butyl alcohol (16·5 g.) were fractionally distilled to remove *iso*propyl alcohol as the binary azeotrope with benzene. During the concentration it was observed that the distillate contained chloride and was acidic. After removal of the solvent the white solid (4·8 g.) was dried at 30—40°/0·1 mm. Analysis confirmed that some replacement of chloride had occurred (Found: Th, 34·7; Cl, 20·3%; Cl : Th, 3·83). The foregoing product (3·2 g.) was dissolved in boiling benzene (5 g.), and the solution allowed to crystallise. After filtration and washing with benzene, the crystalline *tetra*-(n-*butyl alcoholate*) (1·97 g.) was dried at room temperature under reduced pressure (Found: Th, 34·8; Cl, 21·0. $ThCl_4$,4C_4H_9·OH requires Th, 34·6; Cl, 21·2%).

(3) *Action of ethylene glycol on the tetra*(iso*propyl alcoholate*). The alcoholate (7·0 g.), ethylene glycol (19 g.), and benzene (60 g.) were azeotropically fractionated. The solvent was finally removed at 115° under reduced pressure, chloride being detected in the distillate. The gummy residue (8·5 g.) was insoluble in benzene, ether, carbon tetrachloride, or light petroleum and thus could not be purified. However, analysis confirmed that replacement of chlorine had occurred and suggested that at least 5 molecules of ethylene glycol were retained as addenda (Found: Th, 31·7; Cl, 16·4%; Cl : Th, 3·38).

(4) *Action of* tert.*-amyl alcohol on the tetra*(iso*propyl alcoholate*). Benzene (20 g.) and *tert.*-amyl alcohol (10 g.) were added to the tetra(*iso*propyl alcoholate) (8·65 g.), and the mixture heated; a vigorous reaction occurred with the evolution of olefin and alkyl chloride.

One of us (M. A. S.) thanks Alexandria University for study-leave.

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Studies of Trifluoroacetic Acid. Part XII. Acyl Trifluoroacetates and their Reactions.*

By E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall.

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Acetyl, benzoyl, and phenylacetyl trifluoroacetates have been made from the corresponding carboxylic acid–trifluoroacetic anhydride mixtures, and by the interaction of the symmetrical carboxylic anhydrides with trifluoroacetic anhydride. Infra-red analysis showed that in these systems the equilibria favour the unsymmetric anhydrides. In general, the reactions of the acyl trifluoroacetates resemble those of carboxylic acid–trifluoroacetic anhydride mixtures, but it appears that the acylating (as distinct from trifluoroacetylating) activity of the latter media is enhanced by the trifluoroacetic acid liberated as the unsymmetric anhydrides are formed.

It is now well established that acylations of hydroxy-compounds, and of reactive aromatic nuclei, by many carboxylic acids can be promoted by trifluoroacetic anhydride. The mechanisms that have been advanced to explain these reactions have postulated the establishment of the following inter-related equilibria:

$$R{\cdot}CO_2H + (CF_3{\cdot}CO)_2O \rightleftharpoons R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad (1)$$

$$R{\cdot}CO_2H + R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 \rightleftharpoons (R{\cdot}CO)_2O + CF_3{\cdot}CO_2H \quad . \quad . \quad . \quad . \quad (2)$$

$$(R{\cdot}CO)_2O + (CF_3{\cdot}CO)_2O \rightleftharpoons 2R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It has been assumed further that the unsymmetric anhydride can ionise to a slight extent into acylium ($R{\cdot}CO^+$) and trifluoroacetate ($CF_3{\cdot}CO_2^-$) ions, the former being the principal acylating species (Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 942; Bourne, Henry, Tatlow, and Tatlow, *J.*, 1952, 4014; Bourne, Randles, Stacey, Tatlow, and Tedder, *J. Amer. Chem. Soc.*, in the press). These postulates are in accord with the earlier experimental results, and also with the recently described additions of carboxylic acid–trifluoroacetic anhydride systems to olefins and to acetylenes (Henne and Tedder, *J.*, 1953, 3628). Other evidence in support of the hypothesis has been obtained from cryoscopic (Morgan, *J. Amer. Chem. Soc.*, 1951, **73**, 860) and conductivity measurements (Randles, Tatlow, and Tedder, *J.*, 1954, 436). Since, however, unsymmetric anhydrides had not been isolated from carboxylic acid–trifluoroacetic anhydride mixtures, we began a further study of three such systems, and we have isolated from them the expected intermediates, and have investigated some of their reactions; we now record these observations. The preparation, from silver trifluoroacetate and the appropriate acyl chloride, of several of these acyl trifluoroacetates was reported recently by Ferris and Emmons (*J. Amer. Chem. Soc.*, 1953, **75**, 232); no reactions of the compounds were described.

Since much of our work has involved acetylation processes, we studied first the system $CH_3{\cdot}CO_2H$–$(CF_3{\cdot}CO)_2O$; direct distillation of such a mixture gave no definite products (see also Morgan, *loc. cit.*). However, the addition of pyridine to acetic acid–trifluoroacetic anhydride in ether caused the precipitation of a solid, which was shown to be pyridinium trifluoroacetate, and distillation of the residue afforded the desired unsymmetric anhydride, acetyl trifluoroacetate. Further, distillation of an equimolar mixture of acetic and trifluoroacetic anhydrides gave only acetyl trifluoroacetate. These results suggested that the unsymmetric anhydride had but little tendency to disproportionate, and this conclusion was amply confirmed by infra-red analysis. Measurements were made of the unsymmetric anhydride itself (it has a characteristic band at 1072 cm.$^{-1}$), and of the rate of its formation from the two symmetric anhydrides [equilibrium (3)]. Other systems analysed were (*a*) $CH_3{\cdot}CO_2H$–$(CF_3{\cdot}CO)_2O$ and $CF_3{\cdot}CO_2H$–$CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$, and (*b*) $(CH_3{\cdot}CO)_2O$–$CF_3{\cdot}CO_2H$ and $CH_3{\cdot}CO_2H$–$CH_3{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$. The strengths of the band at 1072 cm.$^{-1}$ and bands due to the symmetric anhydrides indicated that acetyl trifluoroacetate was present in

* Part XI, *J.*, 1954, 1941.

equilibrium (3) to the extent of *ca.* 97% of the maximum possible concentration, in systems of type (*a*) to the extent of *ca.* 95%, and in type (*b*) to about 40%. These results are given in Table 1.

Treatment of benzoic acid–trifluoroacetic anhydride, in ether, with pyridine, and distillation of the filtrate, afforded benzoyl trifluoroacetate. Also, direct distillation of benzoic acid–trifluoroacetic anhydride gave first trifluoroacetic acid, and then the unsymmetric anhydride; in addition, the latter was made by distillation of an equimolar mixture of benzoic and trifluoroacetic anhydrides. Application of the last two processes enabled phenylacetyl trifluoroacetate to be prepared, and it appears that each of the three methods constitutes a fairly general process for the synthesis of acyl trifluoroacetates, and, probably, of other acyl perhalogenocarboxylates also. Infra-red measurements on benzoyl and phenylacetyl trifluoroacetates confirmed the earlier conclusions. Many unsymmetric anhydrides are known to disproportionate fairly readily (Emery and Gold, *J.*, 1950, 1443, and earlier references quoted therein; Brown and Trotter, *J.*, 1951, 87); however, the stability of acyl trifluoroacetates during distillation was noted by Ferris and Emmons (*loc. cit.*), though they found that disproportionation was catalysed by silver trifluoroacetate.

Reactions of acetyl trifluoroacetate with a number of hydroxy-compounds gave acetyl esters in good yield (see Table 2). However, with some of the lower aliphatic alcohols the reaction was more complex than this, both acetates and trifluoroacetates being formed. In these cases, since the ester products were liquid, they were converted into the corresponding anilides with anilinomagnesium iodide, according to Hardy's procedure (*J.*, 1936, 398; it was shown that ethyl acetate and ethyl trifluoroacetate gave acetanilide and trifluoroacetanilide, respectively, in this way in excellent yield). The mixture of anilides was then separated chromatographically on an alumina column. Though the total yield of anilides obtained was not quantitative, averaging *ca.* 65%, the method gave a general indication of the relative proportions of acetyl and trifluoroacetyl esters originally produced. In Table 3 are recorded the proportions of acetyl and trifluoroacetyl esters formed in the reaction of acetyl trifluoroacetate with *n*-, *sec.*-, and *tert.*-butyl alcohol, and in the first case the effect of the prior addition of trifluoroacetic acid to the unsymmetric anhydride. The decrease in the proportion of trifluoroacetate in the products, both with increased substitution of the hydroxylated carbon of the butanol, and as trifluoroacetic acid was added in the reaction with the primary alcohol, is noteworthy.

The reaction of acetyl trifluoroacetate with thiophen gave the 2-acetyl derivative, whilst with phenetole (see Table 4) *p*-ethoxyacetophenone was formed in moderate yield (30%) after 46 hr. The use of nitromethane as a solvent gave the same yield in only 3 hr., but addition of sodium trifluoroacetate or acetate to the anhydride prevented ketone formation, whilst acetic acid had little apparent effect. A mixture of acetyl trifluoroacetate and trifluoroacetic acid, however, gave an excellent yield (90%) of ketone in only 3 hr., 1 mol. of acid being necessary to give the best results.

With aniline, acetyl trifluoroacetate gave mainly trifluoroacetanilide, together with a little acetanilide (10%). The latter yield was increased (to 25%) when nitromethane was employed as a solvent. The unsymmetric anhydride and aniline in excess of trifluoroacetic acid gave almost pure trifluoroacetanilide, only a trace (0·5%) of acetanilide being detected.

Benzoyl trifluoroacetate appears to have more tendency to effect trifluoroacetylation than does acetyl trifluoroacetate. Phenols readily gave benzoate esters, but only the trifluoroacetate was obtained with *p*-nitrobenzyl alcohol, though the benzoate was formed when trifluoroacetic acid was added to the anhydride. Trifluoroacetanilide only was detected in the product of the reaction with aniline, and from anisole no ketone was obtained, though *p*-methoxybenzophenone was formed when trifluoroacetic acid was present.

Phenylacetyl trifluoroacetate seems to occupy an intermediate position. Again, phenols gave the phenylacetates almost exclusively, but with *p*-nitrobenzyl alcohol some phenylacetate was isolated, and the presence of a strong acid in the mother-liquors suggested that the trifluoroacetate had been formed as well.

The results obtained so far show that acyl trifluoroacetates ($R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$) can be

obtained from carboxylic acid–trifluoroacetic anhydride mixtures, and that they can function, in many cases, as acylating agents, *i.e.*, for the introduction of R·CO–. However, they are also trifluoroacetylating agents in some cases. Further work on their reactions is in progress to confirm and extend the preliminary results, the mode of attack on different types of hydroxy-compounds under varying conditions being of particular interest. Whilst we prefer to await the results of these further investigations before forming definite conclusions on the reaction mechanisms utilised by acyl trifluoroacetate and carboxylic acid–trifluoroacetic anhydride systems, it appears that our earlier hypotheses are largely in accord with the present observations. The existence of acyl trifluoroacetates in the equilibrium mixtures seems to be established. Tentatively, we suggest that the reactions of these unsymmetric anhydrides themselves may be explained if it is assumed, in accordance with the electronic theory, that in the molecular form they are principally trifluoroacetylating agents [cf. the work of Emery and Gold (*J.*, 1950, **1443**, **1447**, **1455**) on anhydrides from acetic and the chloroacetic acids], whilst the alternative type of acylation is due largely to the acylium ion ($R{\cdot}CO^+$). Thus, the amines and the lower primary alcohols may be simultaneously acylated by the ion and trifluoroacetylated by the molecular anhydride, which, of course, is present in much greater concentration, whilst with the more complex alcohols, the phenols, and aromatic compounds reaction with the latter species may be too slow to be important. The effects of bases and of nitromethane on the reactions of the acyl trifluoroacetates resemble those with $R{\cdot}CO_2H$–$(CF_3{\cdot}CO)_2O$ (Bourne, Henry, Tatlow, and Tatlow; Bourne, Randles, Stacey, Tatlow, and Tedder, *locc. cit.*) and may be explained similarly. Though acyl trifluoroacetates are present in $R{\cdot}CO_2H$–$(CF_3{\cdot}CO)_2O$ mixtures and the reactivity of the latter may arise principally from their presence, it seems clear that the trifluoroacetic acid also produced enhances considerably the acylating activity of these anhydrides. Quantitative work on the various aspects of the problem is necessary before these tentative ideas can be established firmly.

Since this manuscript was prepared a note has appeared in which Emmons, McCallum, and Ferris (*J. Amer. Chem. Soc.*, 1953, **75**, 6047) describe the preparation of several acyl trifluoroacetates by distillation of carboxylic acid–trifluoroacetic anhydride mixtures. Infra-red measurements were used to show that acyl trifluoroacetates were formed almost quantitatively when certain carboxylic acids were treated with trifluoroacetic anhydride. The frequencies employed for this analysis were in the ranges 688—714 cm.$^{-1}$ and 1832—1873 cm.$^{-1}$. No reactions of the materials were reported.

Experimental

Unless otherwise stated, dry reagents and anhydrous conditions were employed.

Acetyl Trifluoroacetate from Acetic Acid–Trifluoroacetic Anhydride.—A mixture of acetic acid (2·10 g.) and trifluoroacetic anhydride (7·41 g.) was kept at 20° for 15 min., and then ether (5 c.c.) was added. Pyridine (2·78 c.c.) in ether (5 c.c.) was introduced dropwise, with cooling and vigorous stirring. The hygroscopic crystalline precipitate, collected by filtration, was *pyridinium trifluoroacetate* (4·63 g.), m. p. 82—83° alone and on admixture with a sample prepared from pyridine and trifluoroacetic acid in ether (Found: F, 28·9%; equiv., 193. $C_7H_6O_2NF_3$ requires F, 29·5%; equiv., 193). Distillation of the filtrate through a short Vigreux column gave ether, and then *acetyl trifluoroacetate* (2·81 g.) as a colourless liquid, b. p. 94—95°, n_D^{25} 1·3253, *d* 1·38 (Found: C, 31·0; H, 2·0; F, 36·1%; equiv., 79. $C_4H_3O_3F_3$ requires C, 30·8; H, 2·0; F, 36·5%; equiv., 78).

To determine the equivalent, the unsymmetric anhydride (0·0461 g.), in water, was titrated (pH meter) against 0·05N-sodium hydroxide. Two end-points were observed, one at pH 3·34, corresponding to neutralisation of the trifluoroacetic acid (5·82 c.c.), and the other at pH 8·55, representing neutralisation of the total acidity (11·65 c.c.). Thus the anhydride gave acetic and trifluoroacetic acids in equimolecular proportions.

Acetyl Trifluoroacetate from Acetic Anhydride–Trifluoroacetic Anhydride.—A mixture of acetic anhydride (1·26 g.) and trifluoroacetic anhydride (2·59 g.), distilled through a short Vigreux column, gave, as the only fraction, acetyl trifluoroacetate (2·32 g.), b. p. 95—96°, n_D^{25} 1·3255 (Found: equiv., 80). The infra-red spectrum of the product, in carbon tetrachloride

solution, was identical, over the frequency range 1000—1250 cm.$^{-1}$, with that of the sample of acetyl trifluoroacetate described above.

Benzoyl Trifluoroacetate from Benzoic Acid–Trifluoroacetic Anhydride.—(*a*) A solution of benzoic acid (5·01 g.) in trifluoroacetic anhydride (9·58 g.) was kept at 40° for 30 min. before ether (5 c.c.) was added, followed by pyridine (3·30 c.c.) in ether (5 c.c.), as before. The pyridinium trifluoroacetate (4·34 g.), m. p. and mixed m. p. 81—82°, was removed by filtration. From the filtrate, benzoyl trifluoroacetate (1·90 g.) was obtained as a colourless oil, b. p. 54°/2·5 mm., n_D^{25} 1·4487 (Found: C, 49·8; H, 2·3%; equiv., 107. Calc. for $C_9H_5O_3F_3$: C, 49·6; H, 2·3%; equiv., 109). Ferris and Emmons (*loc. cit.*) gave b. p. 57—58°/1·7 mm., n_D^{20} 1·4524.

(*b*) A solution of benzoic acid (2·50 g.) in trifluoroacetic anhydride (4·86 g.) was kept at 40° for 30 min., and the liberated trifluoroacetic acid was removed under diminished pressure. The residual liquid was distilled to give benzoyl trifluoroacetate (2·23 g.), b. p. 55—56°/3·8 mm., n_D^{25} 1·4486 (Found: equiv., 109).

Benzoyl Trifluoroacetate from Benzoic Anhydride–Trifluoroacetic Anhydride.—A solution of benzoic anhydride (4·65 g.) in trifluoroacetic anhydride (4·33 g.) was kept at 40° for 90 min., and then distilled, to give benzoyl trifluoroacetate (5·40 g.), b. p. 56—57°/3·5 mm., n_D^{25} 1·4488. The infra-red spectra of all three samples of benzoyl trifluoroacetate, in carbon tetrachloride solution, were identical over the frequency range 1000—1250 cm.$^{-1}$.

Phenylacetyl Trifluoroacetate from Phenylacetic Acid–Trifluoroacetic Anhydride.—A solution of phenylacetic acid (3·00 g.) in trifluoroacetic anhydride (5·62 g.) was kept at 50° for 20 min., and the liberated trifluoroacetic acid was removed under diminished pressure. Distillation of the residue gave phenylacetyl trifluoroacetate (1·32 g.) as a colourless oil, b. p. 98°/15 mm., n_D^{25} 1·4422 (Found: C, 51·8; H, 3·0%; equiv., 118. Calc. for $C_{10}H_7O_3F_3$: C, 51·7; H, 3·0%; equiv., 116). Ferris and Emmons (*loc. cit.*) gave b. p. 57—58°/0·3 mm., n_D^{20} 1·4445.

Potentiometric titration of the unsymmetric anhydride (0·0447 g.) against 0·05N-sodium hydroxide, as before, required 3·76 c.c. for neutralisation of the trifluoroacetic acid (end-point, pH 3·53), and another 3·79 c.c. for neutralisation of the phenylacetic acid (end-point, pH 8·55).

Phenylacetyl Trifluoroacetate from Phenylacetic Anhydride–Trifluoroacetic Anhydride.—A solution of phenylacetic anhydride (2·99 g.) in trifluoroacetic anhydride (3·04 g.) was kept at 50° for 1 hr., before being distilled to give phenylacetyl trifluoroacetate (2·38 g.), b. p. 98°/15 mm., n_D^{25} 1·4422 (Found: equiv., 116). The infra-red spectrum of this compound, in carbon tetrachloride solution, was identical, over the frequency range 1000—1250 cm.$^{-1}$, with that of the sample mentioned above.

Infra-red Spectra.—(*a*) The infra-red spectra of acetic anhydride, of trifluoroacetic anhydride, and of acetyl trifluoroacetate in carbon tetrachloride (concentration *ca.* 0·05M) were determined over the range 1000—1250 cm.$^{-1}$, by use of a Grubb-Parsons spectrometer with a rock-salt prism. The absorption band (at 1121 cm.$^{-1}$) of acetic anhydride, and the band (at 1041 cm.$^{-1}$) of trifluoroacetic anhydride, were entirely absent from the spectrum of acetyl trifluoro-

TABLE 1.

Original system (mol.)					Time after mixing	Components found (mol.)		
Ac_2O	AcOH	$(CF_3{\cdot}CO)_2O$	$CF_3{\cdot}CO_2H$	$Ac{\cdot}O{\cdot}CO{\cdot}CF_3$		Ac_2O (1121 cm.$^{-1}$)	$(CF_3{\cdot}CO)_2O$ (1041 cm.$^{-1}$)	$Ac{\cdot}O{\cdot}CO{\cdot}CF_3$ (1072 cm.$^{-1}$)
0·5	—	0·5	—	—	5 min.	0·12	0·10	0·75
0·5	—	0·5	—	—	15 min.	0·04	0·05	0·90
0·5	—	0·5	—	—	18 hr.	0·03	Nil	0·94
0·5	—	0·5	—	—	14 days	0·01	Nil	0·98
—	1·0	1·0	—	—	2 hr.	0·04	Nil	0·95
—	—	—	1·0	1·0	2 hr.	0·04	Nil	0·95
1·0	—	—	1·0	—	2 hr.	0·60	Nil	0·41
—	1·0	—	—	1·0	2 hr.	0·60	Nil	0·39

acetate, which itself showed a characteristic strong absorption band at 1072 cm.$^{-1}$. The calculated optical densities (1 mole/l. in a cell of thickness *ca.* 0·1 mm.) of the appropriate solutions (*ca.* 0·05M in CCl_4) were then used to estimate, by comparison, the proportion of each of these anhydride components in the following systems: acetic anhydride–trifluoroacetic anhydride, acetic acid–trifluoroacetic anhydride, acetyl trifluoroacetate–trifluoroacetic acid, acetic anhydride–trifluoroacetic acid, and acetyl trifluoroacetate–acetic acid. The results are recorded in Table 1. Acetic and trifluoroacetic acids did not show absorption peaks which interfered with those mentioned above. The accuracy of the method is estimated at ±5%.

(*b*) The infra-red spectrum of benzoyl trifluoroacetate in carbon tetrachloride solution, determined over the same range of frequencies, showed a characteristic strong absorption band at 1086 cm.$^{-1}$. Comparative measurements of optical density showed that benzoyl trifluoroacetate was formed almost quantitatively when benzoic acid was dissolved in trifluoroacetic anhydride.

(*c*) The infra-red spectrum of phenylacetyl trifluoroacetate in carbon tetrachloride solution showed a characteristic absorption band at 1100 cm.$^{-1}$, which was entirely absent from the spectra of phenylacetic and trifluoroacetic anhydride.

Acetylations of Hydroxy-compounds with Acetyl Trifluoroacetate.—The hydroxy-compound (1 mol.) was treated with the unsymmetric anhydride (1·5 mol. per hydroxy-group) at *ca.* 20° for 30 min., and the mixture was poured into excess of sodium hydrogen carbonate solution, which was then extracted with chloroform. The extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving a residue, which crystallised from aqueous alcohol. Three samples of the anhydride were used: (A), prepared as above, by using acetic acid–trifluoroacetic anhydride–pyridine; (B), prepared as above by distillation of an equimolecular mixture of acetic and trifluoroacetic anhydrides; and (C), which was simply an equimolecular mixture of acetic and trifluoroacetic anhydrides. The results are recorded in Table 2 for acetylations of *p*-nitrobenzyl alcohol, methyl α- and β-D-glucopyranoside, D-mannitol, and β-naphthol.

TABLE 2.

		Properties of product		
Ester produced	Anhydride sample	Yield (%)	M. p. and mixed m. p.	$[\alpha]_D^{20}$ in $CHCl_3$ (*c*, 1·0—2·8)
p-Nitrobenzyl acetate	A	80	77—78°	—
	B	75	78	—
	C	84	78	—
Methyl α-D-glucoside tetra-acetate	A	63	100—101	+129°
Methyl β-D-glucoside tetra-acetate	C	64	104	−19·1
D-Mannitol hexa-acetate	C	79	123—124	+25·1
β-Naphthyl acetate	A	81	70	—
	B	76	69	—
	C	81	69—70	—

Reactions of Acetyl Trifluoroacetate with the Butanols.—The alcohol (*ca.* 1·4 g.) in ether (3·0 c.c.) was treated with the unsymmetric anhydride (3·78 g.) and, after 30 min. at *ca.* 20°, ether (30 c.c.) was added. The solution was washed quickly with dilute aqueous sodium hydroxide (0·08N; the calculated volume for neutralisation of the liberated acid and the excess of anhydride was used; the pH of the aqueous phase was then *ca.* 7), then with water, dried ($MgSO_4$), and filtered. Most of the ether was removed by distillation through a 1′ column packed with Dixon gauze spirals. The residual solution was added to anilinomagnesium iodide which had been prepared from magnesium (1·0 g.), methyl iodide (2·9 c.c.), ether (20 c.c.), and aniline (4·0 c.c.), and the mixture was refluxed for 40 min. Water (10 c.c.) was added very cautiously down the condenser, followed by dilute hydrochloric acid. The ethereal layer and extracts of the aqueous phase were dried ($MgSO_4$), filtered, and evaporated. The residual anilides were separated chromatographically, and purified, as described later. The results obtained with *n*-, *sec.*-, and *tert.*-butanol, and from a reaction with *n*-butanol in which acetyl trifluoroacetate–trifluoroacetic acid was used, are given in Table 3.

TABLE 3.

Butanol		$CF_3 \cdot CO_2H$	Product	
Isomer	G.	(g.)	(*a*) Acetanilide (mol.)	(*b*) Trifluoroacetanilide (mol.)
n	1·46	—	0·11	0·51
n	1·45	2·75	0·45	0·14
sec.	1·43	—	0·39	0·21
tert.	1·44	—	0·67	0·02

M. p. and mixed m. p. (*a*) 114°, (*b*) 88—89° in all cases.

Reaction of Acetyl Trifluoroacetate with Aniline.—(*a*) A solution of aniline (0·523 g.) and acetyl trifluoroacetate (1·06 g., 1·20 mol.) in ether (6 c.c.) was kept at *ca.* 20° for 10 min., diluted with ether (30 c.c.), washed with sodium hydrogen carbonate solution, and then with water, dried ($MgSO_4$), and evaporated. The residue was dissolved in benzene, and subjected to chromatographic separation on a column (15 × 2·5 cm.) of alkali-free aluminium oxide. The

column was eluted with benzene, and then with ether–ethanol (1 : 1, by vol.). Evaporation of the benzene solution, and recrystallisation of the residue from light petroleum (b. p. 60—80°), gave trifluoroacetanilide (0·58 mol.), m. p. and mixed m. p. 88—89°. The solute from the ether–ethanol, recrystallised from light petroleum (b. p. 80—100°), gave acetanilide (0·10 mol.), m. p. and mixed m. p. 114°.

(*b*) The experiment was repeated, with nitromethane (4 c.c.) instead of ether (6 c.c.) during the initial reaction. The products were trifluoroacetanilide (0·36 mol.) and acetanilide (0·25 mol.).

(*c*) When the experiment was repeated with trifluoroacetic acid (3 c.c.) instead of ether (6 c.c.) during the initial reaction, the products were trifluoroacetanilide (0·81 mol.) and acetanilide (0·005 mol.).

Acetyl Trifluoroacetate in Ketone Synthesis.—(a) p-*Ethoxyacetophenone.* A mixture of phenetole (0·483 g.) and acetyl trifluoroacetate (0·94 g.; 1·50 mol.) was kept at 10—15° for 18 hr. After dilution of the solution with water (1 c.c.), and neutralisation with sodium hydroxide, the ketone was isolated as its semicarbazone (21%), m. p. 182° (Found: C, 59·9; H, 6·9. Calc. for $C_{11}H_{15}O_2N_3$: C, 59·7; H, 6·8%). Unger (*Annalen*, 1933, **504**, 267) gave m. p. 181·5°.

The experiment was repeated with the same quantities of phenetole and acetyl trifluoroacetate, but with different reaction times, and in the presence of certain other compounds (see Table 4).

TABLE 4.

Addend												
Formula	—	—	—	$CH_3{\cdot}CO_2H$			$CF_3{\cdot}CO_2H$		$CH_3{\cdot}CO_2Na$	$CF_3{\cdot}CO_2Na$	$CH_3{\cdot}NO_2$
Mol.	—	—	—	1·50			0·45	1·50	1·50	1·50	19
Reaction time (hr.) ...	3	18	46	3	16	46	3	3	48	48	3
Yield (%)	0	21	30	11	15	33	45	90	0	0	29

(b) 2-*Acetylthiophen.* A mixture of thiophen (0·26 g.) and acetyl trifluoroacetate (0·75 g.) was kept at 45° for 2 hr., diluted with water (1 c.c.), and neutralised with sodium hydroxide. The ketone was isolated as its semicarbazone (88%), m. p. 189—190° (Found: C, 46·2; H, 5·0. Calc. for $C_7H_9ON_3S$: C, 45·9; H, 5·0%). Steinkopf and Jaffé (*Annalen*, 1917, **413**, 333) gave m. p. 190—191°.

Reaction of Benzoyl Trifluoroacetate with Hydroxy-compounds.—(a) *Phenol.* Treatment of phenol (0·256 g.) with benzoyl trifluoroacetate (0·877 g.) at 60° for 30 min., and isolation of the product as for acetate esters, gave phenyl benzoate (80%), m. p. and mixed m. p. 68°.

(b) β-*Naphthol.* In the same way, β-naphthol (0·300 g.) and benzoyl trifluoroacetate (0·644 g.) afforded β-naphthyl benzoate (88%), m. p. and mixed m. p. 105°.

(c) p-*Nitrobenzyl alcohol.* *p*-Nitrobenzyl alcohol (0·303 g.) was treated with benzoyl trifluoroacetate (0·603 g.), as before, and the oil which remained on evaporation of the chloroform extract was recrystallised from light petroleum (b. p. 40—60°) to give *p*-nitrobenzyl trifluoroacetate (46%), m. p. and mixed m. p. 46—47°. The rest of the product could not be purified; no *p*-nitrobenzyl benzoate could be isolated.

Treatment of *p*-nitrobenzyl alcohol (0·294 g.) with a mixture of benzoyl trifluoroacetate (0·603 g.) and trifluoroacetic acid (0·447 g.) at 60° for 30 min., isolation of the product as before, and crystallisation from aqueous alcohol, gave *p*-nitrobenzyl benzoate (80%), m. p. and mixed m. p. 89°.

Reaction of Benzoyl Trifluoroacetate with Aniline.—A solution of benzoyl trifluoroacetate (1·47 g., 1·2 mol.) and aniline (0·515 g.) in ether (4 c.c.) was kept at 20° for 1 hr., diluted with ether (30 c.c.), and washed, etc., as before. Recrystallisation of the product from light petroleum (b. p. 60—80°) afforded trifluoroacetanilide (0·75 mol.), m. p. and mixed m. p. 88—89°; no benzanilide was detected.

p-*Methoxybenzophenone.*—Anisole (0·25 g) was treated with a mixture of benzoyl trifluoroacetate (0·754 g.) and trifluoroacetic acid (0·447 g.) at 60° for 5 hr., before being poured into aqueous sodium hydrogen carbonate, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated; recrystallisation of the residue from light petroleum (b. p. 60—80°) gave *p*-methoxybenzophenone (64%), m. p. and mixed m. p. 61—62°.

In a second experiment, from which the trifluoroacetic acid was omitted, no residue was obtained from the chloroform extract.

Reaction of Phenylacetyl Trifluoroacetate with Hydroxy-compounds.—(a) *Phenol.* Treatment of phenol (0·203 g.) with phenylacetyl trifluoroacetate (0·600 g.) at 20° for 30 min., and isolation of the ester in the usual way, afforded phenyl phenylacetate (73%), m. p. and mixed m. p. 41°.

(b) p-*Cresol.* In the same way, *p*-cresol (0·205 g.) and phenylacetyl trifluoroacetate (0·510 g.) gave *p*-tolyl phenylacetate (84%), m. p. and mixed m. p. 74—75°.

(c) p-*Nitrobenzyl alcohol.* Likewise, *p*-nitrobenzyl alcohol (0·200 g.) and phenylacetyl trifluoroacetate (0·364 g.) yielded *p*-nitrobenzyl phenylacetate (36%), m. p. and mixed m. p. 64°. The aqueous-alcoholic mother-liquors from the crystallisation were titrated against 0·05N-sodium hydroxide (9·03 c.c. required). This acidity was probably due to trifluoroacetic acid liberated on hydrolysis of *p*-nitrobenzyl trifluoroacetate (cf. Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367).

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Digitalis Glucosides. Part VII. The Structure of the Digitalis Anhydrogenins and the Orientation of the Hydroxy-groups in Digoxigenin and Gitoxigenin.*

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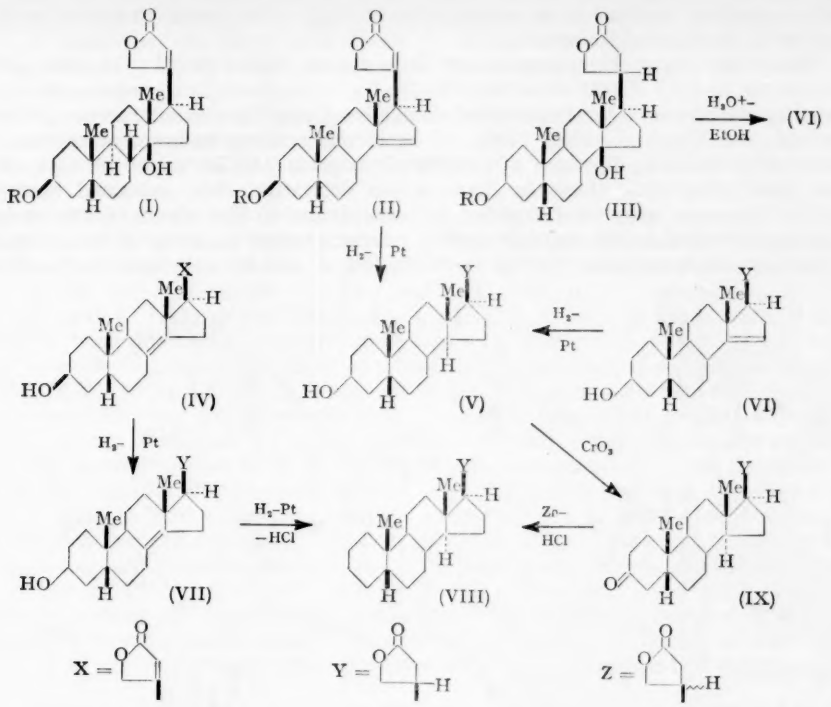
Hydrogenation experiments and spectral studies on the anhydrodigitoxigenins and anhydrodigoxigenins have shown that the dextrorotatory " α "-anhydrogenins are unsaturated at the 8 : 14-position and that the lævorotatory " β "-anhydrogenins are the 14 : 15-unsaturated isomerides. Adynerigenin is shown to be " α "-anhydrogitoxigenin. Evidence is cited for the α-orientation of the 16-hydroxy-group in gitoxigenin and for the β-orientation of the 3-hydroxy-group in digoxigenin. Structures are proposed for the anhydro-*iso*gitoxigenic acids. Four cardanolides differing in configuration at $C_{(14)}$, $C_{(17)}$, and $C_{(20)}$ are described. The mechanism of the formation of the anhydrogenins, which is relevant to the controversy on the mechanism of unimolecular reactions (Dewar, *Ann. Reports*, 1951, **48**, 121), is discussed.

A general mechanism for the chromic acid oxidation of olefins is outlined.

IN Parts II, IV, and VI (refs. *c*, *e*, *f*; for references cited thus, see p. 2013) the preparation of pairs of isomeric anhydrogenins from digitoxigenin (I*a*) and digoxigenin (X*a*) was described. It was suggested that the isomers differed in the location of the nuclear double bond which was introduced on removal of the 14-hydroxy-group and could therefore be at position 8 : 14 or 14 : 15 (steroid numbering). The proof (ref. *o*) that the lævorotatory " β "-anhydrodigoxigenin had the 14 : 15-unsaturated structure (XI) therefore established the alternative 8 : 14-unsaturated structure for the dextrorotatory " α "-anhydrogenins. A double bond position 14 : 15 is readily hydrogenated, whilst an 8 : 14-double bond is inert to hydrogenation under neutral conditions; in the presence of mineral acid partial migration of double bonds takes place with consequent hydrogenation. Tschesche's report (*Z. physiol. Chem.*, 1933, **222**, 50) that 3-β-acetoxy-5α-card-8(14) : 20(22)-dienolide (then called " β "-dianhydrouzarigenin acetate) was hydrogenated under neutral conditions with the uptake of three molecules of hydrogen therefore led Fieser and Fieser (" Natural Products related to Phenanthrene," 3rd Edn., Reinhold Publ. Corpn., 1949, p. 534) to suggest that the dextrorotatory " α "-anhydrogenins contained a nuclear 14 : 15-double bond, the difference from the lævorotatory " β "-anhydrogenins then being ascribed to inversion at a nearby centre. Tschesche's experimental work does not, in our opinion, warrant this conclusion as no hydrogenation product was isolated. The report by Shah, Meyer, and Reichstein (*Pharm. Acta Helv.*, 1949, **24**, 113) that Tschesche's acetate absorbs only one mol. of hydrogen, although doubtless correct, suffers from the same objection.

* Part VI, *J.*, 1936, 354. The present paper is also regarded as " Elimination Reactions. Part III " (Part II, Cardwell, *J.*, 1951, 2442).



	M. p.	$[\alpha]_{Hg}$	$[\alpha]_D$	Refs.		M. p.	$[\alpha]_{Hg}$	$[\alpha]_D$	Refs.
Ia; R = H	252°	+21° M	+17° M	*h*, *r*	IV	234°	+44° M	+39° M	*e*, *i*
Ib; R = Ac	217	+19 C	+21 C	*h*, *r*	V	167	+26 M	+21 M	*a*, *g*
IIa; R = H	202	−17 M	−13 M	*e*, *q*	VI	185°	+49 M	+42 M	*a*, *h*
IIb; R = Ac	185	—	−18 C	*p*, *s*	VII(*a*)	168	+47 M	+40 M	*a*
			−12 M		VII(*b*)	170	—	+32 C	*k*
IIIa; R = H	226	+20 M	+17 M	*a*, *h*	VIII	195	+38 C	+34 C	*a*, *h*, *j*, *l*
IIIb; R = Ac	178	—	+14 C	*n*	IX	240	+44 C	+38 C	*a*, *g*, *k*, *l*

C = chloroform; M = methanol.

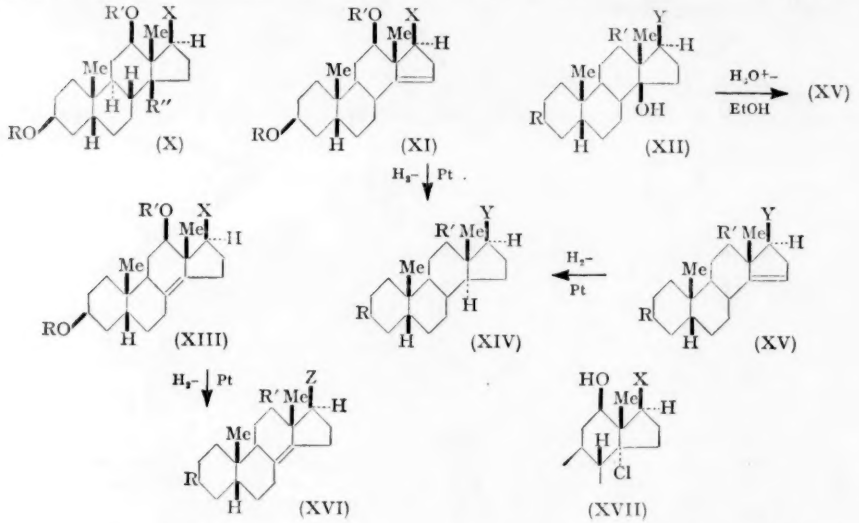
a, This work. *b*, Smith, *J.*, 1930, 508. *c*, *Idem*, *J.*, 1930, 2478. *d*, *Idem*, *J.*, 1931, **23**. *e*, *Idem*, *J.*, 1935, 1050, 1305. *f*, *Idem*, *J.*, 1936, 354. *g*, Windaus and Freese, *Ber.*, 1925, **58**, 2503. *h*, Windaus and Stein, *Ber.*, 1928, **61**, 2436. *i*, Jacobs and Elderfield, *J. Biol. Chem.*, 1933, **100**, 671. *j*, Tschesche and Bohle, *Ber.*, 1936, **69**, 793. *k*, *Idem*, *Ber.*, 1938, **71**, 654. *l*, Neumann, *Ber.*, 1937, **70**, 1547; Fleury and Neumann, *Klin. Woch.*, 1935, **14**, 562. *m*, Tschesche, Bohle, and Neumann, *Ber.*, 1938, **71**, 1927. *n*, Meyer, *Helv. Chim. Acta*, 1946, **29**, 718. *o*, Plattner and Heusser, *Helv. Chim. Acta*, 1946, **29**, 727. *p*, Hunziker and Reichstein, *ibid.*, 1945, **28**, 1472. *q*, Helfenberger and Reichstein, *ibid.*, 1948, **31**, 1470. *r*, Rangaswami and Reichstein, *ibid.*, 1949, **32**, 939. *s*, Rheiner, Hunger, and Reichstein, *ibid.*, 1952, **35**, 687. *t*, Plattner, Ruzicka, and Pataki, *ibid.*, 1945, **28**, 389. *u*, Plattner, Ruzicka, Heusser, and Meier, *ibid.*, 1946, **29**, 2023. *v*, Schindler and Reichstein, *ibid.*, 1952, **35**, 442. *w*, Meyer, *ibid.*, 1946, **29**, 1580. *x*, Tamura, Kobayashi, and Tokita, *Japan. Med. J.*, 1948, **1**, 206.

To remove this confusion we now describe hydrogenation experiments on the anhydrodigitoxigenins and digoxigenins carried out by the senior author in 1934, which, with later spectral evidence, conclusively establish the 8 : 14- and the 14 : 15-structure for the " α "- and " β "-anhydrogenins respectively.

The hydrogenation experiments (see Charts) show that the " α "-anhydrogenins absorb only one mol. of hydrogen, to give dihydro-" α "-anhydrogenins. Dihydro-" α "-anhydrodigitoxigenin (VII*a*) is clearly identical with tetrahydroanhydroadynerigenin (VII*b*) which by hydrogenation under acid conditions has been converted into derivatives of tetrahydro-β-anhydrodigitoxigenin (VIII and IX) (refs. *k*, *m*) (we discuss the structure of

adynerigenin below). This establishes that the isomeric anhydrogenins have the same nuclear structure and the same configuration at $C_{(17)}$. They must therefore be 8 : 14- and 14 : 15-unsaturated isomerides.

Ultra-violet absorption measurements in methanol (2060—2200 Å; Unicam spectrophotometer, model S.P. 500) show that dihydro-" α "-anhydrodigitoxigenin has the absorption characteristics of a tetrasubstituted double bond (see Experimental section) (Bladon, Henbest, and Wood, *J.*, 1952, 2737). As *apo*cholic acid shows lower absorption than cholest-8(14)-en-3β-ol, dihydro-" α "-anhydrodigoxigenin (XVI*a*) might be expected to show lower absorption than the digitoxigenin derivative. The measured absorption however was even lower than expected and was similar to that shown by cholest-5-ene. This suggestive but ambiguous result made it necessary to test the nature of the unsaturated systems by other methods. Colour reactions (Légal, and tetranitromethane) confirmed



	M. p.	$[\alpha]_{Hg}$	$[\alpha]_D$	Refs.
X*a*; R = R′ = H, R″ = OH	222°	+27° M	+20° E +18 A	*a*, *b*
X*b*; R = R′ = Ac, R″ = OH	221	+61 M	+49 C	*c*
XI*a*; R = R′ = H	182	−16 M	−13 M	*c*
XI*b*; R = H; R′ = Ac.....	199	+32 C	+26 C	*a*
XI*c*; R = R′ = Ac	199	+39 M	+30 C	*c*, *o*
XII*a*; R = R′ = β-OH	215	+23 M	+19 M	*a*, *c*
XII*b*; R = R′ = β-OAc	224	+30 M	+24 C	*b*, *l*
XII*c*; R = R′ = O:	243	+120 C	+98 C	*a*, *e*
XIII*a*; R = R′ = H	192	+46 M	+38 M	*a*, *f*
XIII*b*; R = Ac, R′ = H	218	—	+31 C	*a*
XIII*c*; R = R′ = Ac	155	+68 M	—	*f*
XIV*a*; R = R′ = β-OH	118	—	+20 C	*t*
XIV*b*; R = R′ = O:	290	+150 C	+132 C	*a*, *j*, *t*
XV*a*; R = R′ = β-OAc	204	—	+52 C	*u*
XV*b*; R = R′ = O:	288	+172 C	+144 C	*a*
XVI*a*; R = R′ = β-OH	218	+81 M	...	*a*
XVI*b*; R = R′ = β-OAc	165	+67 M	—	*a*
XVI*c*; R = R′ = O:	105	+103 M	—	*a*

A = acetone; C = chloroform; E = ethanol; M = methanol.

the absence of the butenolide ring in the dihydro- and tetrahydro-derivatives and the presence of a double bond in the dihydro-" α "-anhydrogenins. Similarly, infra-red spectroscopy (these measurements form part of a larger investigation by Dr. F. B. Strauss and the junior author which will be reported later) has shown replacement of the butenolide doublet at 5·72 μ (1750 cm.$^{-1}$) and 6·13 μ (1630 cm.$^{-1}$) by the butanolide peak at 5·64 μ

(1770 cm.$^{-1}$) in the reduced anhydrogenins. In addition the " β "-anhydrogenins showed absorption at 12·0 μ (835 cm.$^{-1}$) to 12·6 μ (795 cm.$^{-1}$) due to the system $>C_{(14)}:C_{(15)}H-$ (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402) which was absent in the parent genins, " α "-anhydrogenins, dihydro-" α "-anhydrogenins, and tetrahydro-" β "-anhydrogenins.

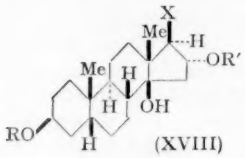
A further objection to the 8 : 14-unsaturated structure for the dextrorotatory " α "-anhydrogenins has been raised by Fieser and Fieser (*op. cit.*). They point out that *apo*cholic acid [3α : 12α-dihydroxychol-8(14)-enoic acid], $[\alpha]_D$ +50°, is less dextrorotatory than its 14 : 15-unsaturated isomeride, $[\alpha]_D$ +60°, in contrast to the 8 : 14-unsaturated anhydrodigoxigenin (XIII*a*) and its 14 : 15-unsaturated isomeride (XI*a*). This divergence is due to the proximity of the polar butenolide ring. When this is reduced to the butanolide ring the optical relation of the " α "- and the " β "-anhydro-isomers is reversed, *viz.*, 3 : 12-dioxo-20β-card-8(14)-enolide * (XVI*c*) and 3 : 12-dioxo-20β-card-14-enolide (XV*b*). Comparison with 3 : 12-dioxo-14α : 20β-cardanolide (XIV*b*) shows that introduction of an 8 : 14-double bond produces a negative change, and a 14 : 15-double bond a slight positive change, as in the similarly substituted *apo*cholic acid series (Barton and Klyne, *Chem. and Ind.*, 1948, 755). In the digitoxigenin series, 3β-hydroxy-20β-card-8(14)-enolide (VII*a*) is similarly less dextrorotatory than 3β-hydroxy-20β-card-14-enolide (VI), but now the saturated compound (V) is less dextrorotatory than either unsaturated isomer. These figures agree (Professor D. H. R. Barton, personal communication) with the observation that the rotation of coprosteryl acetate, $[\alpha]_D$ +27° (calculated from the observed value for coprosterol), is slightly less positive than that of coprost-8(14)-enyl acetate, $[\alpha]_D$ +31° (Windaus and Zühlsdorff, *Annalen*, 1938, **536**, 204). Clearly the 8 : 14-double bond is too near substituents in rings B, C, and D for there to be any standard value for the molecular increment of rotation on introduction of this double bond. The fact that there is agreement both in the dihydrodigitoxigenin and in the digoxigenin series with values obtained from similarly nuclear-substituted steroids is even more convincing evidence for the location of the double bond than if a standard value independent of substitution applied.

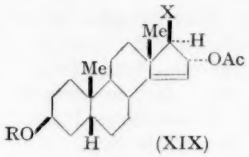
Anhydrogitoxigenins and Adynerigenin.—Owing to the lability of the 16-hydroxy-group, " α "-anhydrogitoxigenin has not yet been prepared by conventional chemical procedures. Dehydration of gitoxigenin derivatives catalysed by dilute acid gives mixtures of the " β "- or 14-anhydrogenin † (XIX) and the 14 : 16-dianhydrogenin † (XXIV) (ref. *l*; Windaus and Westphal, *Nachr. Ges. Wiss. Göttingen*, 1925, 78) which may contain small quantities of " α "-anhydrogenins, whilst concentrated hydrochloric acid or dry hydrogen chloride in acetone at low temperatures gives only the dianhydrogenin (Windaus and Schwarte, *Ber.*, 1925, **58**, 1515; Cloetta, *Arch. expt. Path. Pharmak.*, 1926, **112**, 261; see also p. 2022 below). However an enzyme in the leaves of *Nerium oleander* can apparently form " α "-anhydrogitoxigenin derivatives, for adynerin (XXI*a*) (a physiologically inactive glycoside) is an " α "-anhydro-derivative of oleandrin (XVIII; R = Oleandrose; R′ =

* The 20β-structure is assigned to the reduced products on the following grounds. *X*-Ray crystallographic studies (personal communication from Mrs. D. Crowfoot Hodgkin) have shown that cholesterol, lumisterol, and calciferol have the same configuration at $C_{(20)}$ which by the Plattner convention (*J.*, 1951, 3536) is designated 20β. The natural nor*allo*cholanoic acids are therefore 20β, whilst the slightly less dextrorotatory 20-*iso*nor*allo*cholanoic acids are 20α (Plattner and Pataki, *Helv. Chim. Acta*, 1943, **26**, 1241; Bergmann and Low, *J. Org. Chem.*, 1947, **12**, 67). We therefore assign the 20β-configuration to the more dextrorotatory of the isomeric dihydrogenins. In the digitoxigenin series transformations lead, as shown in the Chart, to the ketone (IX). This was prepared by Windaus and Stein (*Ber.*, 1928, **61**, 2436) by dehydration of dihydrodigitoxigenin, m. p. 200°, to " β "-anhydrodihydrodigitoxigenin, m. p. 181°, followed by hydrogenation and oxidation. Our crude dihydrodigitoxigenin (III*a*), prepared similarly, had m. p. 203°, $[\alpha]_D$ +18°, and gave an anhydro-compound (VI). Our dihydrogenin must be 20β, for its rotation agrees with that of the more dextrorotatory dihydrodigitoxigenin acetate (III*b*) and not with that of the isomeric 20α-acetate, $[\alpha]_D$ +8° (ref. *n*). In the digoxigenin series, 20β-tetrahydroanhydrodigoxigenone (XIV*b*) and the 20α-isomeride, $[\alpha]_D$ +123°, have been prepared from synthetic 3α : 12α-dihydroxy-14α-card-20(22)-enolide (ref. *l*). The former is identical with the product from " β "-anhydrodigoxigenin. By analogy, dihydro-" α "-anhydrodigoxigenin should also have the 20β-configuration but this has not been proved.

† In this series, by custom, the prefix " anhydro " refers to loss of water with formation of a double bond, and not to presence of an oxide ring as in general nomenclature. Numeral(s) attached to this " anhydro "-prefix refer to the position of the double bond thus introduced.

Ac) (ref. *l*). On hydrolysis it gives adynerigenin (XXI*b*) (ref. *k*). Tschesche and Bohle (ref. *k*) were led, by their conviction that this genin formed only a monoacetate (undescribed), to formulate it as 3β : 14-dihydroxycard-8 : 20(22)-dienolide (XXV). This structure does not explain the chemistry of adynerigenin (cf. Fieser and Fieser, *op. cit.*,


(XVIII)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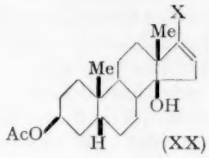
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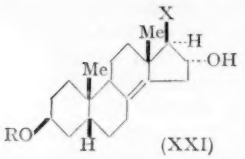
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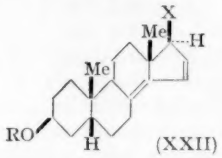
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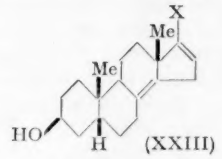
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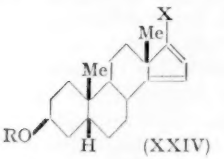
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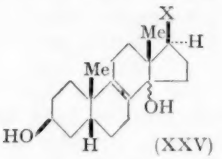
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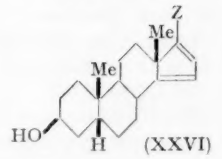
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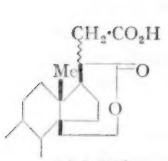
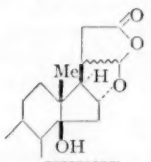
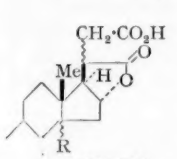

(XXVII)


(XXVIII)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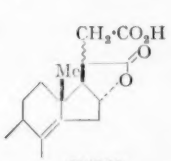
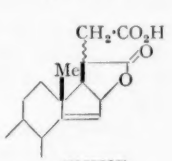

(XXX)


(XXXI)

	M. p.	$[\alpha]_{Hg}$	$[\alpha]_D$	Refs.
XVIII*a*; R = R′ = H	228°	+39° M	+33° M	*d*, *v*
XVIII*b*; R = R′ = Ac	252	−3 M	−8 C	*v*
XVIII*c*; R = Ac; R′ = H	232	—	+33 C	*a*, *l*, *w*, *x*
XVIII*d*; R = H; R′ = Ac	223	—	−9 M	*l*
XIX*a*; R = Glucose	208	—	±0 P	*m*
XIX*b*; R = H	259	—	—	*m*
XIX*c*; R = H	262	—	—	*l*
XIX*d*; R = Ac	184	—	—	*m*
XIX*e*; R = Ac	168	—	—	*m*
XX	207	—	+81 C	*a*, *n*
XXI*a*; R = Oleandrose	234	—	+8 P	*l*
XXI*b*; R = H	238	—	+18 P	*l*
XXII*a*; R = H	176	—	−109 C	*k*
XXII*b*; R = Ac	152	—	−106	*k*, *l*
XXIII	235	—	+147 C	*k*
XXIV*a*; R = H	212	+737 M	+580 M	*a*, *v*
XXIV*b*; R = Ac	208	+574 M	+502 C	*a*
XXVI	210	+276 M	+227 M	*a*

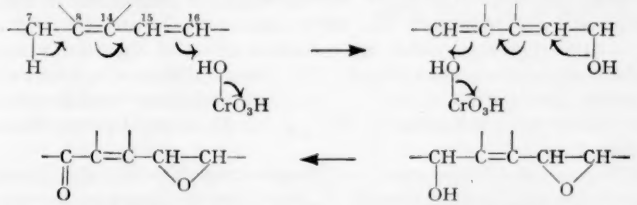
C = Chloroform; M = methanol; P = pyridine.

p. 541; Turner, *Chem. Reviews*, 1948, **43**, 1) or its physiological inactivity. Its formulation as 8(14)-anhydrogitoxigenin removes these difficulties. Thus the anhydroadynerigenin ($\lambda_{max.}$ 2470 Å) formed on dehydration catalysed by dilute acid becomes 8(14) : 15-dianhydrogitoxigenin (XXII*a*) (calc. $\lambda_{max.}$ 2440 Å), isomerised by cold concentrated hydrochloric acid to 8(14) : 16-dianhydrogitoxigenin (XXIII) ($\lambda_{max.}$ 2800 Å; cf. 16-anhydrogitoxigenin acetate (XX), $\lambda_{max.}$ 2730 Å, ref. *w*). Hydrogenation of anhydroadynerigenin gave tetraanhydrohydroadynerigenin (VII*b*), which is clearly identical with dihydro-" α "-anhydro-

digitoxigenin (VII*a*), this identity being confirmed by its hydrogenation under acid conditions and oxidation to tetrahydro-" β "-anhydrodigitoxigenone (IX) and to 14α : 20β-cardanolide (VIII). In addition these experiments suggest an α-orientation of the 16-hydroxy-group in adynerigenin, for although the 8(14) : 16-dianhydrogen in (XXIII) is more stable than the 8(14) : 15-unsaturated isomeride, the latter is first formed on mild dehydration. There must therefore be a mechanistic barrier to dehydration towards $C_{(17)}$. This may be, in an ionic mechanism favouring *trans*-elimination, the *cis*-arrangement of the 17α-hydrogen atom and the 16-hydroxyl group.* Reichstein (*Angew. Chem.*, 1951, **63**, 412; and personal communication) depicted the 16-hydroxy-group in gitoxigenin as α-orientated, the ready loss of acetic acid from gitoxigenin diacetate on alumina to give 16-anhydrogitoxigenin acetate (XX) (ref. *w*) suggesting a *cis*-relation of the eliminated groups in this heterogeneous reaction. The preparation of 15-anhydrogitoxigenin by solvolysis of a 16-gitoxigenin toluene-*p*-sulphonate would have completed the proof of the α-orientation at $C_{(16)}$. In fact, however, the sole product isolated (see p. 2022) was the 16 : 17-unsaturated isomer; this cannot, nevertheless, be cited as evidence for β-orientation at $C_{(16)}$ as we are uncertain whether the elimination occurred before or during chromatographic purification. We think it very unlikely that the glycosides of *Nerium oleander* are derived from genins isomeric at $C_{(16)}$ (the main glycoside, oleandrin, is a gitoxigenin derivative), and thus depict gitoxigenin as 3β : 16α : 14-trihydroxycard-20(22)-enolide (XVIII*a*).†

The above proof of structure of the anhydrogenins allows an interpretation of certain aspects of their chemistry.

Chromic Acid Oxidation of the " α "-Anhydrogenins.—Steroids containing a ditertiary double bond, *e.g.*, cholest-8(14)-enyl acetate, are readily oxidised by chromic acid to 7- or 15-oxo-8(14)-enyl oxides (Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1513). A similar by-product was isolated (ref. *e*) on oxidation of " α "-anhydrodigitoxigenin and is now shown to be $C_{23}H_{28}O_5$.‡ In Part VI (ref. *f*) isolation of a by-product from the oxidation of " α "-anhydrodigoxigenin was also recorded and this was probably a 7- or 15-oxo-8(14)-enyl oxide. The same type of structure may also be assigned to the substance $C_{23}H_{30-32}O_5$ isolated in low yield (ref. *k*) on oxidation of tetrahydroanhydroadynerigenin. The compound $C_{23}H_{26-28}O_5$ ($\lambda_{max.}$ 2520 Å) isolated on oxidation of anhydroadynerigenin is of more interest. If it is assumed by analogy with action of chromyl chloride



on olefins (Cristol and Eilar, *J. Amer. Chem. Soc.*, 1950, **72**, 4353) that the elements of OH^+ are added to the negative end of the conjugated system, an expected product would be the 7-oxo-8(14)-enyl 15 : 16-oxide [(calc. $\lambda_{max.}$ 2590 Å; cf. 5-hydroxy-ergost-8(14)-ene-3 : 7-dione, $\lambda_{max.}$, 2540 Å; Dannenberg, *Abhandl. preuss. Akad. Wiss.*, 1939, **21**, 3). [Other possible structures by this mechanism would be 16-oxo-14-enyl 7 : 8(or 8 : 9)-oxides

* This argument would be invalidated if (XXIII) were not the major product of dehydration, but the experimental details allow no decision on this point. The strained nature of the fused ring system in *iso*gitoxigenin as depicted in (XXVIII) makes such a reservation necessary (Professor C. W. Shoppee, personal communication).

† For the same reason we formulate neriantogenin (XIX*b*) as " β "-anhydro-oleandrigenin (XIX*c*), the melting points of the genins and acetates (XIX*d* and *e*) suggesting identity. Tschesche, Bohle, and Neumann (ref. *m*) give no experimental evidence to support their statement that the acetates are different. Unfortunately no measurements of optical rotation were made.

‡ Kiliani's anhydrodigitoxigenin, m. p. 251—220° (*Ber.*, 1920, **53**, 246), called " β " (ref. *g*), was clearly substantially our " α "(8 : 14-unsaturated)-isomer. The derived toxigenone, m. p. 260° (C, 75·8; H, 8·0%), was probably a mixture of " α "- and " β "-anhydrodigitoxigenone (C, 77·9; H, 8·5%), and the keto-oxide, m. p. 273° (C, 71·8; H, 7·3%).

(cf. Barton, Holness, Overton, and Rosenfelder, *J.*, 1952, 3751).] This type of mechanism may be general for the chromic acid oxidation of olefins and explains the various products obtained in the oxidation of 7 : 8-, 8 : 9-, and 8 : 14-unsaturated steroids (Fieser and Fieser, *op. cit.*, p. 227 *et seq.*) and removes the unlikely reactions (dehydration of α-hydroxy-ketones, and formation of keto-oxides from αβ-unsaturated ketones) postulated in other mechanisms.

Mechanism of Dehydration.—The precise mechanism of, and degree of stereochemical control in, substitution and elimination reactions, assumed to be unimolecular by close analogies, has been the subject of much discussion (cf. Dewar, *Ann. Reports*, 1951, **48**, 121). The reactions of the 14β-hydroxy-group in these genins indicate that the stereochemical control normally associated with bimolecular reactions (replacement with inversion and *trans*-elimination) (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252; Hückel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191) is largely operative. Thus " β "-anhydrogenins are the sole product of dehydration with phosphorus oxychloride and pyridine (ref. *p*), the intermediate phosphorus ester (X; R = R = Ac, R'' = O·$POCl_2$) (cf. Gerrard, *J.*, 1950, 2088) undergoing *trans*-elimination. Dehydration of the genins with dilute acids gives mixtures in which the " β "-anhydrogenins predominate, despite the fact that the " α "-anhydrogenins are more stable (Jacobs and Elderfield, *J. Biol. Chem.*, 1936, **113**, 611). On treatment with concentrated hydrochloric acid, digoxigenin gives, by substitution with inversion, the 14α-chloro-compound (XVII), which on dissolution in hot methanol undergoes *trans*-elimination to give a quantitative yield of " α "-anhydrodigoxigenin (XIII*a*) (ref. *f*). All these reactions show a degree of stereochemical control which indicates that the ionising group has not fully separated before elimination or substitution takes place.

14α-Chlorogitoxigenin cannot be prepared from gitoxigenin as the 16-hydroxy-group is very labile; when this lability is reduced by saturation of the butenolide ring, as in *iso*gitoxigenin (XXVIII) and *iso*gitoxigenic acid (XXIX; R = β-OH), 14α-chloro-compounds can be formed (Jacobs and Gustus, *J. Biol. Chem.*, 1929, **82**, 403; 1930, **86**, 199). The 14α-orientation in chloro*iso*gitoxigenin is proved by its ready elimination, giving 8(14)-anhydro*iso*gitoxigenin, whose resistance to catalytic hydrogenation is now explained. Similarly, 14α-chloro*iso*gitoxigenic acid (XXIX; R = *a*-Cl), on dissolution in dilute aqueous ammonia (unimolecular conditions), gave the hydrate of 8(14)-anhydro-*iso*gitoxigenic acid, $[\alpha]_D$ +27° (XXX).* In contrast, on dissolution in aqueous sodium hydroxide (bimolecular elimination) the chloro-acid gave 14-anhydro*iso*gitoxigenic acid (XXXI), $[\alpha]_D$ +61°. The control by the inductive effect of the 16-oxygen atom in the bimolecular elimination is not unexpected. The great difference in rotation between the 8 : 14- and the 14 : 15-unsaturated acids shows how sensitive the contribution of these nuclear double bonds is to substitution at $C_{(16)}$ (cf. Mancera, Barton, Rosenkranz, and Djerassi, *J.*, 1952, 1021).

Structure of Digoxin and Digoxigenin.—Although crystalline digoxin (the tridigitoxoside of digoxigenin) was isolated in 1930 (Smith, *J.*, 1930, 508) and has been in clinical use in this country since 1933 † (*Brit. Med. J.*, 1933, 295, 364) the generally accepted proof of its structure is unsatisfactory. It has been degraded to a methyl 3 : 12-dihydroxyetianate (A), $[\alpha]_{Hg}$ +46°, $[\alpha]_D$ +39° (Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 828). This substance did not give a melting-point depression with material (B), $[\alpha]_{Hg}$ +49°, obtained by hydrogenation of methyl 3 : 12-dioxoetianate and was oxidised to this diketone (Mason and Hoehn, *J. Amer. Chem. Soc.*, 1938, **60**, 2824; 1939, **61**, 1614). Nor did it

* Jacobs and Gustus called this acid γ-*iso*gitoxigenic acid and assumed that it was related to *iso*-gitoxigenic acid, $[\alpha]_D$ −50°, in the same way as γ-*iso*digitoxigenic acid, $[\alpha]_D$ +60°, is to α-*iso*digitoxigenic acid (XXVII), $[\alpha]_D$ −31°. This cannot be the case. The latter change does not involve any rearrangement of the nuclear skeleton, as shown by the identity of the derived digitoxanol diacid with a product resulting from reduction of 14-anhydro*iso*gitoxigenic acid; it must therefore involve movement of the lactone ring from $C_{(14)}$ to $C_{(15)}$ or $C_{(16)}$. As *iso*gitoxigenic acid does not have a lactone ring at $C_{(14)}$ it cannot undergo this change. The difference in the rotational changes in the two series supports this interpretation.

† Reichstein (*Angew. Chem.*, 1951, **63**, 412) (see also Fieser and Fieser, *op cit.*, p. 573) is incorrect in describing the use of digitoxin in America in 1945 as the first departure from digitalis galenical preparations.

depress the melting point of (C), $[\alpha]_D$ +52°, obtained from the reduction of authentic 3α-hydroxy-12-oxoetianate (Wenner and Reichstein, *Helv. Chim. Acta*, 1944, **27**, 965). Substance (C) is certainly the 3α : 12β-dihydroxy-compound as it differed from the known 3α : 12α-compound. In this field, optical rotations are probably of more significance than melting points and we note that the rotations of (A) and (B) are significantly different from that of (C) and in the direction to be expected if (A) and (B) are the 3β : 12β-dihydroxyetianates. Professor Reichstein (*loc. cit.*, and personal communication) has reached the same conclusion and has kindly informed us that he is now investigating the isomeric 3 : 12-dihydroxyetianates. We have not therefore probed this question by repetition of the degradation to an etianate but have carried out partial acetylation and hydrolysis experiments. Treatment of digoxigenin with one equivalent of acetic anhydride in cold pyridine or boiling benzene gave digoxigenin and digoxigenin diacetate with no trace of monoacetate. With β-anhydrodigoxigenin however we were able to isolate the 12-monoacetate (XI*b*) with ease. With α-anhydrodigoxigenin a complex mixture was obtained from which, after chromatography, the 3-monoacetate (XIII*b*) was isolated by virtue of its insolubility but we have no doubt that some of the 12-monoacetate was also formed. Hydrolysis experiments were confined to digoxigenin diacetate. Hydrazine hydrate in methanol at room temperature (24 hours) did not affect the diacetate. Slow addition of 0·1N-sodium hydroxide to a hot aqueous-ethanolic solution of the diacetate gave a large acidic fraction from which some diacetate could be recovered, thus confirming that this reagent opens the butenolide ring, at least in part, without isomerisation to the aldehyde (cf. Paist, Blout, Uhle, and Elderfield, *J. Org. Chem.*, 1941, **6**, 373). The neutral fraction gave some unchanged diacetate, but the mother-liquors contained the 3-monoacetate as oxidation with chromic acid gave the 3-acetoxy-12-oxo-compound, $[\alpha]_D$ +113°. The orientation of these new products was determined by rotational analysis, the rotation change on acetylation or oxidation of the 12-hydroxy-group being so large that it could not be confused with reactions involving a 3α- or 3β-hydroxy-group. The derived molecular-rotation increments for acetylation of the 3-hydroxy-group were +28° and −15°. Comparison with the standard values for 3β (+17° ± 17°) and 3α (+83° ± 30°) (Barton, *J.*, 1946, 1116) strongly suggests a 3β-orientation for the hydroxy-group in digoxigenin. In addition, we noted that the 12-ketone 3-acetate from digoxigenin and 3-monoacetate of the " α "-anhydrogenin showed, in paraffin mulls, a complex acetate band at 8 μ. A complex band in carbon disulphide is characteristic of 3β-acetoxycholane derivatives (Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1951, **73**, 3215); in paraffin mull a 3β-acetoxycholane derivative may show a simple band but the inverse, *i.e.*, a complex band with a 3α-acetoxycholane derivative, has not yet been observed (Schindler and Reichstein, *Helv. Chim. Acta*, 1952, **35**, 730). A simple band would therefore not have been informative, but the complex bands observed are, we think, significant. The conclusion that digoxigenin is 3β : 12β : 14-trihydroxycard-20(22)-enolide and not the 3α : 12β-compound as usually depicted is strengthened by the realisation that the former orientation alone allows a satisfactory explanation of the partial acetylation and hydrolysis experiments. Thus the combination of a non-reactive 3β(" polar ")-hydroxy-group with a reactive 12β(" equatorial ")-hydroxy-group, the latter being hindered by the 14β-hydroxy-group and ring D in digoxigenin but not in the " β "-anhydrogenin, explains the results. In the " α "-anhydrogenin the 8 : 14-double bond modifies the conformation of ring C in a manner whose consequences have not yet been evaluated. Rigid proof of the structure of digoxigenin must now await Professor Reichstein's current experiments, the weight of the existing evidence strongly favouring the new 3β : 12β-hydroxy-structure and thus bringing digoxigenin into line with all the heart poisons of proved structure. [The day after submission of this manuscript, Professor Reichstein informed us that the 3β : 12β-configuration had been established (see Pataki, Meyer, and Reichstein, *Experientia*, 1953, **9**, 253; *Helv. Chim. Acta*, 1953, **36**, 1295; Taylor, *J.*, 1953, 3325).]

The Experimental section also includes the proof of the common nuclear structure of digitoxigenin and digoxigenin by their conversion into deoxycardanolides (VIII). In this we were anticipated, but as our products were crystallised to constant rotation

experimental details are given. In the gitoxigenin series two further isomeric 3β-hydroxycardanolides were isolated. By analogy with the reduction of 16-anhydrogitoxigenin (XX) (ref. *w*) the three isomers obtained are all probably 17α-cardanolides.

Experimental

Hydrogenations were carried out at atmospheric pressure in ethanol with previously reduced platinum oxide. In oxidations Kiliani's chromic acid solution (water, 400 g.; concentrated sulphuric acid, 80 g.; chromic oxide, 53 g.) was used except where stated. Products were isolated by pouring into water and filtration if crystalline. If oily, the product was extracted with chloroform and washed with dilute sulphuric acid and/or aqueous sodium hydrogen carbonate as appropriate and dried ($MgSO_4$). In the determination of optical rotations, *c* ranged from 0·1 to 5. In the earlier work, where crystallisation was frequently to constant rotation, estimated errors have not been given. Except where stated, rotations were determined in chloroform. In ultra-violet measurements the substance in methanol in a 1-mm. cell was examined in a Unicam model S.P. 500. In chromatography, columns of acid-washed alumina were prepared in benzene and eluted with benzene–chloroform.

Dihydro-"α"-anhydrodigitoxigenin (VII).—"α"-Anhydrodigitoxigenin (0·1 g.) absorbed hydrogen (7·3 c.c.; 1 mol., 6·3 c.c.) in 25 min. The *dihydrogenin* crystallised from aqueous methanol in needles, m. p. 172°, $[\alpha]_{Hg}^{20}$ +46·5°, $[\alpha]_{D}^{20}$ +39·7° in MeOH (Found: C, 76·7; H, 9·6. $C_{23}H_{34}O_3$ requires C, 76·6; H, 10·1%). It gave a negative Légal reaction and a yellow colour with tetranitromethane and had absorption max. at 2060 (ε 10,500), 2100, (ε 8800), 2140 (ε 6100), and 2180 Å (ε 4500). A mixture with tetrahydro-"β"-anhydrodigitoxigenin (m. p. 167°) melted at 155°.

8:14-*Epoxy*-3:7(or 15)-*dioxocard*-20(22)-*enolide*.—The *by-product* (ref. *e*) from the chromic acid oxidation of "α"-anhydrodigitoxigenin was crystallized to constant m. p. 273° (Found: C, 71·4; H, 7·5. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

Tetrahydro-"β"-anhydrodigitoxigenin (V).—"β"-Anhydrodigitoxigenin (0·179 g.) absorbed hydrogen (24·2 c.c.; 2 mol., 22·6 c.c.) in 1½ hr. The product crystallised from methanol in needles, m. p. 167°, $[\alpha]_{Hg}^{20}$ +26·3°, $[\alpha]_{D}^{20}$ +21·3° in MeOH (ref. *g*). It gave negative Légal and tetranitromethane reactions.

Tetrahydro-"β"-anhydrodigitoxigenone (IX).—"β"-Anhydrodigitoxigenin (1·0 g.) absorbed hydrogen (116·8 c.c.; 2 mol., 126·6 c.c.) in 1 hr. The product, in aqueous acetic acid (80%; 20 c.c.), was treated with chromic acid solution (5 c.c.) for 20 min. The ketone crystallized readily from methanol and from ethyl acetate and had m. p. 235°, $[\alpha]_{Hg}^{20}$ +43·9°, $[\alpha]_{D}^{20}$ +38·0° (ref. *g*, *h*, *l*).

14α:20β-*Cardanolide* (VIII).—The foregoing ketone (0·3 g.), acetic acid (15 c.c.), concentrated hydrochloric acid (10 c.c.), and amalgamated zinc (4 g.) were heated on a water-bath for 6 hr. The oily product slowly crystallised. After two crystallisations from methanol and one each from ethanol and acetone it melted at 188—190° (Found: C, 80·3; H, 10·3. Calc. for $C_{23}H_{36}O_2$: C, 80·2; H, 10·5%) (refs. *h*, *j*, *l*).

Dihydrodigitoxigenin (III*a*).—Digitoxigenin (1·0 g.) absorbed hydrogen (65 c.c.; 1 mol., 60 c.c.) in 1 hr. On concentration the solution was acid to litmus, suggesting that some βγ-isomeride had been hydrogenated with ring opening. The product after one crystallisation from methanol had m. p. 203°, $[\alpha]_{D}^{20}$ +18·6° in MeOH, raised by crystallisation from benzene and then ethyl acetate to m. p. 226°, $[\alpha]_{Hg}^{20}$ +19·9°, $[\alpha]_{D}^{20}$ +17·1° in MeOH (ref. *h*). The more soluble crops had lower rotations.

"β"-*Anhydrodihydrodigitoxigenin* (VI).—The preceding dihydrogenin (0·85 g.) in ethanol (12 c.c.) was refluxed with 10% sulphuric acid (12 c.c.) for 0·5 hr. The anhydrodihydrogenin crystallised from ethyl acetate with a molecule of solvent (Found: Loss at 100° *in vacuo*, 19·0. Calc. for $C_{23}H_{32}O_3,C_4H_8O_2$: 19·8%), m. p. 185°, $[\alpha]_{Hg}^{20}$ +49·0°, $[\alpha]_{D}^{20}$ +41·5° in MeOH (an anhydrous specimen had m. p. 187°) (ref. *h*).

Dihydro-"α"-anhydrodigoxigenin (XVI*a*).—"α"-Anhydrodigoxigenin dihydrate (2 g.; 1·1 g.; 0·22 g.) absorbed hydrogen (111 c.c.; 67·9 c.c.; 16·6 c.c.: 1 mol., 110 c.c.; 60·4 c.c.; 12·1 c.c. respectively). *Dihydro-"α"-anhydrodigoxigenin* crystallised from methanol in needles, m. p. 218°, $[\alpha]_{Hg}^{16}$ +81·4° in MeOH (Found: C, 73·9; H, 9·2. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·2. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%). It gave a negative Légal reaction, a yellow colour with tetranitromethane, and absorption max. at 2060 (ε 4600), 2100 (ε 3400), 2140 (ε 2420), and 2180 Å (ε 1270). The *diacetate* (XVI*b*) crystallised from aqueous methanol in needles,

m. p. 165°, $[\alpha]_{Hg}^{20}$ +66·7° in MeOH (Found: C, 70·7; H, 8·5; Ac, 19·5. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·4; Ac, 18·6%).

Dihydro-"α"-anhydrodigoxigenone (XVI*c*).—The above dihydrogenin (0·6 g.) in aqueous acetic acid (90%; 10 c.c.) was treated with chromic acid solution (3 c.c.) with ice-cooling. After 0·5 hr. the solution was diluted with water. The ketone separated as a *monohydrate*, in needles, m. p. 105° (Found: C, 71·1; H, 8·4; loss, 4·1. $C_{23}H_{30}O_4,H_2O$ requires C, 71·1; H, 8·3; H_2O, 4·6%). The anhydrous *form* had m. p. 105°, $[\alpha]_{Hg}^{20}$ +103° in MeOH (Found: C, 74·3; H, 8·4. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·2%). A *monosemicarbazone* (presumably 3) separated overnight, on treatment of the ketone with aqueous-methanolic semicarbazide acetate, in needles, m.p. 238° (decomp.) (Found: N, 10·2. $C_{24}H_{33}O_4N_3$ requires N, 9·8%).

Tetrahydro-"β"-anhydrodigoxigenone (XIV*b*).—"β"-Anhydrodigoxigenin (1·35 g.) absorbed hydrogen (161 c.c.; 2 mol., 163 c.c.) in 5 hr. The product in aqueous acetic acid (80%; 15 c.c.) was treated with chromic acid solution (6·7 c.c.). After 0·5 hr. at room temperature the mixture was diluted with water. The ketone crystallised from aqueous ethanol in needles, m. p. 288°, $[\alpha]_{Hg}^{20}$ +150°, $[\alpha]_D^{20}$ +140° (Found: C, 74·2; H, 8·5. Calc. for $C_{23}H_{32}O_4$: C, 74·2; H, 8·7%) (ref. *j*, *t*).

12-*Oxo*-14α : 20β-*cardanolide*.—The preceding diketone (0·25 g.), concentrated hydrochloric acid (5 c.c.), and amalgamated zinc (3 g.) were heated under reflux for 5 hr. Ethanol (5 c.c.), hydrochloric acid (5 c.c.), and zinc (3 g.) were added and refluxing was continued for 2 hr. The product crystallised from aqueous acetone in rods, m. p. 217—218°, $[\alpha]_{Hg}^{20}$ +134° (Found: C, 77·5; H, 9·8. Calc. for $C_{23}H_{34}O_3$: C, 77·1; H, 9·6%) (cf. Tschesche and Bohle, *Ber.*, 1936, **69**, 2497).

14α : 20β-*Cardanolide* (VIII).—The diketone (1·02 g.), acetic acid (24 c.c.), concentrated hydrochloric acid (12 c.c.), and amalgamated zinc (10 g.) were heated under reflux for 1·5 hr. Further additions of acetic acid (46 c.c.), hydrochloric acid (20 c.c.), and zinc (20 g.) were made during 5 hr. After a total of 8·5 hours' refluxing the product was isolated in the usual manner. The first crystalline crop (0·5 g.) had $[\alpha]_{Hg}$ +33° and the second $[\alpha]_{Hg}$ +75°, indicating that, even after the vigorous treatment, reduction was not complete. The first crop, after four recrystallisations from ethyl acetate, gave 51 mg. of the pure saturated lactone, m. p. 195°, $[\alpha]_{Hg}^{20}$ +38·0°, $[\alpha]_D^{20}$ +33·0° (Found: C, 80·0; H, 10·1. Calc. for $C_{23}H_{36}O_2$: C, 80·2; H, 10·5%).

"β"-*Anhydrodihydrodigoxigenone* (XV*b*).—Dihydrodigoxigenone (XII*c*), $[\alpha]_D^{20}$ +98° (0·95 g.) (from dihydrodigoxigenin, $[\alpha]_D^{20}$ = +19° in MeOH), in ethanol (20 c.c.) and aqueous 10% sulphuric acid (20 c.c.) were heated on a water-bath for 2·5 hr. The *product* crystallised from aqueous ethanol in needles, m. p. 288°, $[\alpha]_{Hg}^{20}$ +172°, $[\alpha]_D^{20}$ +144° (Found: C, 74·3; H, 8·3. $C_{23}H_{30}O_4$ requires C, 74·6; H, 8·2%). Further crops from the mother-liquors had much lower rotations, *viz.*, $[\alpha]_{Hg}$ +105°, $[\alpha]_D$ +86°, suggesting the presence of the dihydro-"α"-anhydro-isomer (XVI*c*).

12β-*Acetoxy*-3β-*hydroxycard*-14 : 20(22)-*dienolide* (XI*b*).—β-Anhydrodigoxigenin (2·287 g.) in pyridine (10 c.c.) was treated with acetic anhydride (0·68 c.c.). The product was chromatographed and the following fractions were collected: (i) 157 mg., $[\alpha]_D$ +10·2°, (ii) 325 mg., (iii) 654 mg., $[\alpha]_D$ +1·4°, (iv) 390 mg., (v) 118 mg., $[\alpha]_D$ −14·4°, (vi) 105 mg., (vii) 197 mg., $[\alpha]_D$ −17·2°, (viii) 261 mg., (ix) 390 mg., $[\alpha]_D$ −12·5°, (x) 278 mg., (xi) 155 mg., $[\alpha]_D$ −11·0°, (xii) 55 mg., $[\alpha]_D$ 0°. Fractions (i) and (ii) on crystallisation from methanol gave the 12-*monoacetate*, m. p. 199—200°, $[\alpha]_D^{20}$ +25·3° ± 1° (Found: C, 72·7; H, 8·5. $C_{25}H_{34}O_5$ requires C, 72·4; H, 8·3%). The infra-red spectrum showed a hydroxyl and an acetate band. When mixed with "β"-anhydrodigoxigenin diacetate (XI*c*) it melted at 160—170°. Fraction (viii) on crystallisation from methanol gave rectangular prisms of "β"-anhydrodigoxigenin, m. p. and mixed m. p. 177—178°. The mother-liquors from fractions (i) and (ii) were combined with (iii) and (iv) and rechromatographed, the following fractions being collected: (*a*) 144 mg., $[\alpha]_D$ +20·8°, (*b*) 136 mg., $[\alpha]_D$ +22·8°, (*c*) 86 mg., $[\alpha]_D$ +26·8°, (*d*) 224 mg., $[\alpha]_D$ −4°, (*e*) 54 mg., $[\alpha]_D$ −24°. Fractions (*a*), (*b*), and (*c*) on crystallisation gave further crops of the 12-monoacetate, m. p. 185—190°, $[\alpha]_D^{16}$ +26·8° ± 1°. Fraction (*e*) gave a further crop of "β"-anhydrodigoxigenin.

3β-*Acetoxy*-12β : 14-*dihydroxycard*-8(14) : 20(22)-*dienolide* (XIII*b*).—"α"-Anhydrodigoxigenin (0·459 g.; $[\alpha]_D^{20}$ +39·3° in MeOH) was acetylated as for the "β"-isomer. Chromatography gave a little diacetate and then a very small fraction (50 mg.) of the 3-*monoacetate*, m. p. 218—225° (from aqueous methanol), $[\alpha]_D^{20}$ +31·3° ± 3° (Found, on a sample dried at 100° *in vacuo*: C, 72·4; H, 8·3. $C_{25}H_{34}O_5$ requires C, 72·4; H, 8·3%). The infra-red spectrum showed a hydroxyl and an acetate band. After the 3-monoacetate mixed fractions were obtained before pure "α"-anhydrogenin was eluted.

3β-*Acetoxy*-14-*hydroxy*-12-*oxocard*-20(22)-*enolide*.—Digoxigenin diacetate (2·4 g.) in aqueous ethanol (50%; 300 c.c.) was slowly treated on a water-bath with aqueous sodium hydroxide (0·1N; 50·5 c.c.). Initial addition of the alkali was at such a rate that the solution was kept near neutral to phenolphthalein. The hydrolysis under such conditions was extremely slow. After concentration under reduced pressure the mixture was extracted with chloroform. The neutral fraction on crystallisation from ethyl acetate gave unchanged digoxigenin diacetate (700 mg.), m. p. and mixed m. p. 232°. The mother-liquors from the diacetate on oxidation with chromic acid and crystallisation from aqueous methanol gave fine needles, m. p. 228—229°, of the *acetoxy-ketone*, $[\alpha]_D^{16}$ +113° ± 1° (Found: C, 69·2; H, 7·9. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%). The infra-red spectrum showed a hydroxyl and butenolide, ketone, and acetate bands; the substance gave a red Légal reaction. The water-soluble fraction on acidification gave, after extraction with chloroform and storage for 24 hr. to complete relactonisation, much digoxigenin diacetate, m. p. and mixed m. p. 230° (positive Légal reaction). Examination of these fractions has not been completed.

Reduction of Anhydrogitoxigenins.—(a) *Dianhydrogitoxigenin*, m. p. 212—213°, $[\alpha]_{Hg}$ +737°, $[\alpha]_D^{21}$ +583° *in* MeOH (XXIV*a*). The combined products from the several hydrogenations of dianhydrogitoxigenin (in all, 5·25 g.) were fractionally crystallised from aqueous methanol. The least-soluble portion, crystallised to constant m. p. and rotation, furnished "β"-3β-*hydroxy*-14ξ : 17ξ : 20ξ-*cardanolide*, m. p. 203°, $[\alpha]_{Hg}^{20}$ +19·0°, $[\alpha]_D^{20}$ +16·3° in MeOH (0·25 g.) (Found: C, 76·5; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%). Other crops, m. p. 165° to 188°, $[\alpha]_{Hg}$ +53° to +87°, may have contained the "α"-isomer as reported by Windaus and Schwarte (*Ber.*, 1925, **58**, 1515). The alkaline washings from these neutral products gave, on acidification and three crystallisations from aqueous methanol, an isomer or mixture of isomers of 3β-*hydroxy*-14ξ : 17ξ : 20ξ-*norcholanoic acid*, m. p. 212° (Found: C, 76·5; H, 10·5. $C_{23}H_{38}O_3$ requires C, 76·2; H, 10·5%). (b) *Dianhydrodihydrogitoxigenin*, $[\alpha]_{Hg}^{20}$ +276°, $[\alpha]_D^{20}$ +227° *in* MeOH (XXVI). The product from the hydrogenation of dianhydrodihydrogitoxigenin (3·87 g.) was fractionally crystallised from aqueous methanol. The more insoluble portions gave "α"-3β-hydroxy-14ξ : 17ξ : 20ξ-cardanolide, m. p. 217—218°, $[\alpha]_{Hg}^{20}$ +85·7°, $[\alpha]_D^{20}$ +72·9° in EtOH (Found: C, 76·7; H, 10·1. Calc. for $C_{23}H_{36}O_3$: C, 76·6; H, 10·1%). Later fractions gave "γ"-3β-*hydroxy*-14ξ : 17ξ : 20ξ-*cardanolide*, m. p. 160°, $[\alpha]_D^{20}$ +52·8° in MeOH (Found: C, 76·8; H, 10·1. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%).

Attempted Preparation of "α"-Anhydrogitoxigenin.—(*a*) Gitoxigenin diacetate (2 g.) was dissolved in ice-cold concentrated hydrochloric acid (40 c.c.) by shaking. After 10 hr. at −5° the solution was poured on ice. The derived product was reacetylated with acetic anhydride and pyridine. Crystallisation from methanol gave dianhydrogitoxigenin acetate, m. p. 207—208°, $[\alpha]_D^{20}$ +502° ± 5°, $[\alpha]_D^{20}$ +574° ± 8° in MeOH. (*b*) Gitoxigenin diacetate (372 mg.) in acetone (10 c.c.) was saturated with hydrogen chloride at −76°. After this mixture had been in a Dewar flask overnight its temperature had reached 0°. After working up as above, crystallisation from methanol gave dianhydrogitoxigenin diacetate, m. p. 206—207°, $[\alpha]_D^{20}$ +500° ± 4°. The mother-liquors from (*a*) and (*b*) were then chromatographed twice; apart from substantial further quantities of the dianhydro-acetate only a few mg. of oil of lower rotation were obtained.

3β-*Acetoxy*-14 : 16α-*dihydroxycard*-20(22)-*enolide* (XVIII*c*).—Gitoxigenin diacetate (10 g.) in ethanol (750 c.c.) and water (500 c.c.) was slowly treated on a water-bath with aqueous 0·1N-sodium hydroxide (220 c.c.). Hydrolysis was much faster than with digoxigenin diacetate and was complete in 10 min. The mixture was concentrated under reduced pressure until copious crystallisation occurred. The product was filtered off and extracted with hot methanol (25 c.c.) (when hydrolysis was incomplete, filtration at this point left solid unchanged diacetate). Evaporation of the methanol and crystallisation of the residue from ethyl acetate gave the 3-monoacetate, m. p. 227—232°, $[\alpha]_D^{15}$ +33·1° ± 1·3°, $\lambda_{max.}$ 2170 Å (ε 16,000); the presence of butenolide and acetate absorption in the infra-red, coupled with a positive Légal reaction, showed that this substance was not a derivative of *iso*gitoxigenin. The above procedure (ref. *l*) was preferable to hydrolysis with potassium carbonate in aqueous dioxan (ref. *w*) whence much unchanged diacetate was recovered.

3β-*Acetoxy*-14-*hydroxycard*-20(22)-*enolide* 16α-*Toluene*-p-*sulphonate*.—The foregoing monoacetate was treated in pyridine with toluene-*p*-sulphonyl chloride at room temperature for 18 hr. The resulting waxy solid, on extraction with hot benzene, left much insoluble unchanged starting material, m. p. 212—220°, $[\alpha]_D^{17}$ +39° ± 2°. The benzene solution deposited a small crop of plates, m. p. 150—155°. Recrystallisation from aqueous methanol gave the *toluene*-p-*sulphonate* as flat prisms, m. p. 155—157°, $[\alpha]_D^{18}$ +39·4° ± 0·5° (Found: C, 67·8; H, 7·8. $C_{32}H_{42}O_7S$ requires C, 67·4; H, 7·4%). In a second experiment the monoacetate was warmed with pyridine and

toluene-*p*-sulphonyl chloride on a water-bath for 20 min. The dark gummy product could not be crystallised then or after solvolysis with hot ethanolic potassium acetate for 4 hr. Chromatography finally gave 16-anhydrogitoxigenin acetate (XX), m. p. 190—192°, $[\alpha]_D^{20}$ +79·5° ± 2° (Found: C, 72·3; H, 8·3. Calc. for $C_{25}H_{34}O_5$: C, 72·4; H, 8·3%).

Analyses were partly by Mr. A. Bennett. Ultra-violet and infra-red spectra were determined by Dr. F. B. Strauss with the technical assistance of Mr. F. H. L. Hastings. This work was completed during the tenure of a Pressed Steel Company Research Fellowship (to H. M. E. C.).

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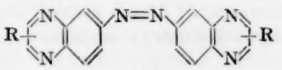
Cinnolines and Other Heterocyclic Types in Relation to the Chemotherapy of Trypanosomiasis. Part IX. Synthesis of Azoquinoxaline Derivatives.*

By C. M. ATKINSON, C. W. BROWN, J. MCINTYRE, and (the late) J. C. E. SIMPSON.

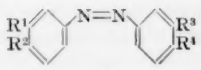
[Reprint Order No. 5071.]

A preparative route to 3 : 3′ : 4 : 4′-tetra-aminoazobenzene is described. Condensation of this compound with butyl glyoxylate gave a mixture of hydroxy-6 : 6′-azoquinoxalines, and thence two pure dichloro-6 : 6′-azoquinoxalines in small yield. Similar condensation of 3 : 4-diaminoazobenzene has given a mixture from which 2(or 3)-hydroxy-6-phenylazoquinoxaline can be isolated directly.

THE activity shown by bis(azocinnolinium salts) against *Trypanosoma congolense* (McIntyre and Simpson, *J.*, 1952, 2606, 2615) led us to consider the extension of this work to include ring systems other than cinnolines. The present communication describes attempts to synthesise the corresponding bisazoquinoxaline derivatives (I; R = NH_2) for conversion into the analogous quaternary salts. Of the general methods available for the preparation of aminoquinoxalines (Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publ. Inc., New York, 1953, p. 263) that involving preparation of the hydroxyquinoxaline (I; R = OH) from the di-*o*-diamine (II; $R^1 = R^2 = R^3 = R^4 = NH_2$) was selected.



(I)



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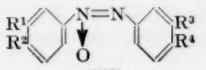

(III)

The key intermediate, 4-amino-2-nitroacetanilide, has been prepared by Chazel (*Ber.*, 1907, **40**, 3177) from *p*-aminoacetanilide by phthaloylation, nitration, and selective hydrolysis of the phthaloyl group. A number of modifications proved necessary for the smooth operation of each of these stages on a much larger scale. We have shown that phthaloylation in an aqueous medium yields roughly equal amounts of *p*-acetamidophenylphthalamic acid and *p*-phthalimidoacetanilide but the latter is exlcusively formed in acetic acid (cf. Vanags and Veinbergs, *Ber.*, 1942, **75**, 1558). Nitration of the phthalimido-compound by Chazel's method was satisfactory on the small scale but in larger preparations unchanged material and a dinitro-compound were isolated: reproducible yields of 2-nitro-4-phthalimidoacetanilide were however obtained by using nitric acid of lower density under controlled conditions. Selective hydrolysis to the amine was effected by Chazel's method. The orientation of the nitro-group which was not established by Chazel follows from deamination of the derived 4-amino-3-nitroazobenzene (see below) to 3-nitroazobenzene (Bamberger and Hübner, *Ber.*, 1903, **36**, 3803).

* Part VIII, *J.*, 1954, 1381.

Oxidation of 4-amino-2-nitroacetanilide with Caro's acid gave results analogous to those with other amines (McIntyre and Simpson, *J.*, 1952, 2606), 4 : 4′-diacetamido-3 : 3′-dinitroazoxybenzene (III; $R^1 = R^3 = NO_2$, $R^2 = R^4 = NHAc$) being the only isolatable product after reaction in acid solution whereas in neutral solution a 56% yield of 2-nitro-4-nitrosoacetanilide was separable from the azoxy-compound. Condensation of 4-amino-2-nitroacetanilide with the derived nitroso-compound gave an almost theoretical yield of the azobenzene derivative (II; $R^1 = R^3 = NO_2$, $R^2 = R^4 = NHAc$), but hydrolysis to the diamine offered some difficulty. The use of alcoholic hydrochloric acid did not give a smooth reaction, and hydrochloric–acetic acid gave a product which was shown to contain partly hydrolysed material (II; $R^1 = R^3 = NO_2$, $R^2 = NHAc$, $R^4 = NH_2$) since reduction yielded an acetamidodiamino-nitroazobenzene as well as the desired tetra-aminoazobenzene. The latter was eventually prepared in high yield by hydrolysis with sulphuric acid to the dinitro-diamine and reduction with sodium hydrogen sulphide.

The mixed hydroxyquinoxalines (I; R = OH) were obtained from 3 : 3′ : 4 : 4′-tetra-aminoazobenzene by reaction with *n*-butyl glyoxylate. Although this reagent has been widely applied by Wolf and his co-workers (*J. Amer. Chem. Soc.*, 1949, **71**, 6) to the synthesis of hydroxyquinoxalines, no convenient method of preparing it is described. We could not reproduce the high yields claimed by Wolf (personal communication) using lead tetra-acetate on *n*-butyl tartrate, but oxidation with sodium periodate provided a good preparative route. The condensation product possessed no definite melting point but the general properties agreed with the representation as (I; R = OH). Phosphoryl chloride and phosphorus pentachloride converted this crude material into a mixture giving, in low yield, two crystalline dichloro-6 : 6′-azoquinoxalines (α and β) by chromatography. Although this result could be reproduced on a small scale, attempts to increase it gave only partly pure crystalline fractions. Attempts to achieve separation of the crude mixture by treatment with phosphorus halides and subsequent phenoxylation gave only a small amount of the α-dichloro-derivative, a result in agreement with later experience (Atkinson, Brown, and Simpson, unpublished work) of the reactivity of simpler quinoxalines.

The possibility of using the azoxy-compounds (as III) as a source of the azo-types was was investigated. The compound (III; $R^1 = R^3 = NO_2$, $R^2 = R^4 = NHAc$) was smoothly hydrolysed to the diamine but an attempt to reduce the latter with sodium hydrogen sulphide gave only 3 : 4 : 3′ : 4′-tetra-aminoazoxybenzene.

Some phenylazo-derivatives were also prepared for use as model compounds; reaction between 2-nitro-4-nitrosoacetanilide and aniline, or 4-amino-2-nitroacetanilide and nitrosobenzene, gave 4-acetamido-3-nitroazobenzene (II; $R^1 = NO_2$, $R^2 = NHAc$, $R^3 = R^4 = H$), readily hydrolysed to the nitro-amine and thence by reduction to 3 : 4-diaminoazobenzene. Condensation of the latter with butyl glyoxylate gave a mixture of 2(and 3)-hydroxy-6-phenylazoquinoxalines, one of which was obtained pure directly by recrystallisation.

Experimental

p-*Aminoacetanilide*.—*p*-Nitroacetanilide (60 g.) in ethanol (600 c.c.) was hydrogenated during 90 min. at 60—70°/40 atm. with 2% palladium–strontium carbonate (4·85 g.). The catalyst was filtered off and the filtrate was treated with charcoal and concentrated to *ca.* 400 c.c., to provide *p*-aminoacetanilide (42 g.), m. p. 163·5—166°; a second-crop (7·9 g.), m. p. 166—167°, was obtained on further evaporation.

p-*Phthalimidoacetanilide*.—*p*-Aminoacetanilide (170 g.) in hot acetic acid (1 l.) was added to a hot stirred solution of phthalic anhydride (170 g.) in acetic acid (1·2 l.). A crystalline solid began to separate almost immediately, and, after 5 hours' refluxing, filtration of the cold reaction mixture gave pure *p*-phthalimidoacetanilide (288 g., 91%), m. p. 287—288°, as colourless needles.

Nitration of p-*Phthalimidoacetanilide*.—(*a*) The compound (60 g.) was added to cooled (ice–salt) nitric acid (240 c.c.; *d* 1·50) at −6° (±1°). After 1 hr. at −6° the mixture was poured on crushed ice (3 l.); the precipitate was collected, washed until acid-free, partially dried (porous plate), and digested for 2 hr. with boiling 95% ethanol (3 l.); the alcohol-soluble fraction (15 g.; m. p. 203—223°), together with an intractable oil formed on removal of solvent, were rejected. The insoluble fraction (24·5 g.), m. p. 240—244°, gave on recrystallisation from

acetic acid pale yellow tabular needles (17·6 g.), m. p. 251—253°, of a *dinitro*-derivative (Found: C, 52·0; H, 3·3; N, 15·3. $C_{16}H_{10}O_7N_4$ requires C, 51·9; H, 2·7; N, 15·1%).

This derivative (16 g.) was kept overnight with aqueous ammonia (400 c.c.; *d* 0·880), and the suspension refluxed for 6 hr. and filtered cold. 4-*Amino*-x : y-*dinitroacetanilide* (10 g.), m. p. 252—254°, crystallised from water in large golden tabular needles (Found: C, 40·3; H, 3·6; N, 23·7. $C_8H_8O_5N_4$ requires C, 40·0; H, 3·4; N, 23·3%).

(*b*) The compound (120 g.) was added during 70 min. to stirred nitric acid (800 c.c.; *d* 1·48—1·49) at −12° to −13°, the mixture held at this temperature for 1 hr., and the clear yellow solution poured on crushed ice (4 l.). The bright yellow solid was washed well and dried over sodium hydroxide *in vacuo*, and the crude solid (135 g.; m. p. 248—250°) was recrystallised from acetic acid (4·5 l.) to provide pure 2-nitro-4-phthalimidoacetanilide (118 g.), m. p. 249—251°.

4-*Amino*-2-*nitroacetanilide*.—The precursor (61 g.; m. p. 249—251°) and aqueous ammonia (1·25 l.; *d* 0·880) were slowly (during 6 hr.) heated with stirring to the b. p. and then refluxed for 2 hr. The dark red solution was treated with carbon and cooled to provide either golden needles or dark red tabular needles, m. p. 163—166°, of the amino-compound.

2-*Nitro*-4-*nitrosoacetanilide*.—A slightly warm (supersaturated) solution of 4-amino-2-nitroacetanilide (6 g.) in dioxan (40 c.c.) was quickly added to a neutralised Caro's acid solution (900 c.c., containing 80 g. of H_2SO_5), and the mixture was shaken for 10 min. The flocculent ochre precipitate was collected and combined with a small second crop which separated after 3 hr. This crude, washed material was digested successively with ethanol–water (3 : 2; 150 c.c., " A ") and hot water and finally recrystallised from acetic acid. 4 : 4′-*Diacetamido*-3 : 3′-*dinitroazoxybenzene* (0·69 g.) formed bright yellow fibrous needles, m. p. 241—242·5° unchanged by recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found: C, 47·85; H, 3·3; N, 21·1. $C_{16}H_{14}O_7N_6$ requires C, 47·75; H, 3·5; N, 20·9%). The same compound (2·5 g.; 50%), m. p. and mixed m. p. 238—240° (needles from acetic acid), was formed by adding a hot aqueous solution of 4-amino-2-nitroacetanilide (5 g. in 350 c.c.) to Caro's acid solution (650 c.c.; 67 g. of H_2SO_5) containing ice and setting the whole aside for 16 hr.

The mixture of green and yellow needles (4·38 g.), m. p. 102—105°, which separated on cooling the aqueous-alcoholic mother-liquor " A " was recrystallised from 50% aqueous alcohol (80 c.c.), to yield pure 2-*nitro*-4-*nitrosoacetanilide* (3·25 g.), m. p. 102·5—105° (green tabular needles from ethanol) (Found: C, 45·8; H, 3·5; N, 20·0. $C_8H_7O_4N_3$ requires C, 45·0; H, 3·4; N, 20·1%).

4 : 4′-*Diacetamido*-3 : 3′-*dinitroazobenzene*.—Slightly warm (supersaturated) solutions of 2-nitro-4-nitrosoacetanilide (3·3 g.) and 4-amino-2-nitroacetanilide (3·3 g.) in acetic acid (25 c.c. each) were mixed and set aside overnight. The precipitate (6 g.), m. p. 274—281°, was collected and recrystallised from acetic acid (2 l.); the *azo*-compound (4·5 g.), m. p. 284—285°, separated as orange needles (Found: C, 50·0; H, 3·7; N, 21·8. $C_{16}H_{14}O_6N_6$ requires C, 49·7; H, 3·8; N, 21·8%).

4 : 4′-*Diamino*-3 : 3′-*dinitroazobenzene*.—4 : 4′-Diacetamido-3 : 3′-dinitroazobenzene (6 g.) was dissolved in concentrated sulphuric acid (110 c.c.) by gentle warming, and water (187·5 c.c.) added with stirring and cooling. The suspension was heated at 100° for ½ hr. and then cooled and the dark blue sulphate was collected and treated with very dilute ammonia solution, to give the crude orange 4 : 4′-*diamino*-3 : 3′-*dinitroazobenzene* (4·45 g.), m. p. 338—339°. Purification could be effected by recrystallisation from phenol–ethanol, but was unnecessary for the subsequent reduction. The recrystallised material consisted of red plates or orange needles, m. p. 340—341° (Found: C, 47·9; H, 4·0; N, 27·6. $C_{12}H_{10}O_4N_6$ requires C, 47·7; H, 3·3; N, 27·8%).

When the hydrolysis was carried out by a refluxing mixture of concentrated hydrochloric acid and acetic acid (25 c.c. of each per g.), and the free base recrystallised from phenol–ethanol an apparently homogeneous product (" B "), m. p. >330°, was obtained.

3 : 3′ : 4 : 4′-*Tetra-aminoazobenzene*.—4 : 4′-Diamino-3 : 3′-dinitroazobenzene (3 g., crude) was heated for 1 hr. with ethanol (30 c.c.) and 26% (w/v) sodium hydrogen sulphide (27 c.c.; freshly prepared), and the crystalline purple solid (2·14 g., 89%), m. p. 252—256° (decomp.), was removed whilst still hot. The pure *tetra-amine*, m. p. 252—256° (decomp.), crystallised as violet needles from aqueous ethanol (Found: C, 59·7; H, 6·0; N, 34·7. $C_{12}H_{14}N_6$ requires C, 59·5; H, 5·8; N, 34·7%).

Similar reduction of the hydrolysis product " B " (above) gave, by fractional recrystallisation from aqueous ethanol, violet needles of 3 : 3′ : 4 : 4′-tetra-aminoazobenzene, m. p. 250° (decomp.) (Found: C, 59·1; H, 6·1%), and dark red, silky needles of 4-*acetamido*-3(or 3′) : 4′-*diamino*-

3′(or 3)-*nitroazobenzene*, m. p. 245—246° (decomp.) (Found: C, 53·7; H, 4·5; N, 26·2. $C_{14}H_{14}O_3N_6$ requires C, 53·5; H, 4·5; N, 26·7%).

Dihydroxy-6 : 6′-*azoquinoxaline*.—A hot solution of 3 : 3′ : 4 : 4′-tetra-aminoazobenzene (1 g.) in ethanol (170 c.c.) and water (90 c.c.) was refluxed with one of *n*-butyl glyoxylate (1·1 g.) in ethanol (5 c.c.) for 6 hr., then cooled, and the brown solid (1·05 g.), m. p. indefinite, was collected. This material was almost insoluble in organic solvents but readily soluble in dilute aqueous sodium hydroxide from which it was reprecipitated in gelatinous form by dilute acids.

Dichloro-6 : 6′-*azoquinoxaline*.—Dihydroxy-6 : 6′-azoquinoxaline (1 g.), phosphoryl chloride (10 c.c.), and phosphorus pentachloride (2 g.) were refluxed for 50 min., the mixture was poured on crushed ice (*ca.* 300 c.c.), and the maroon solid (1·1 g.), m. p. 250°, was collected. This was extracted with hot benzene (3 × 80 c.c.), and the red extract evaporated to dryness; this solid (0·77 g.) was dissolved in cold benzene (300 c.c.) and poured down a column of Type "H" alumina (100 g.). Elution was continued with pure dry benzene; the first three (100 c.c.) fractions contained (α)-*dichloro*-6 : 6′-*azoquinoxaline*, m. p. 276—277°, which separated from benzene in long red needles (Found: C, 54·1; H, 2·25; N, 24·25; Cl, 20·8. $C_{16}H_8N_6Cl_2$ requires C, 54·1; H, 2·3; N, 23·7; Cl, 20·0%). This was followed by two fractions which consisted of material of m. p. *ca.* 200° and then by (β)-*dichloro*-6 : 6′-*azoquinoxaline*, m. p. 270—272°, which crystallised from benzene in short, orange-red needles (Found: C, 53·75; H, 2·5; N, 23·55; Cl, 20·65%). The mixed m. p. between the α- and β-isomers was 232—245°. (*Note*: It is suspected that the success of this separation is critically dependent on the activity of the alumina used.)

Further elution with benzene gave a negligible amount of material and the solid eluted by chloroform did not crystallise. The combined α- and β-fractions (formed in approximately equal amount) accounted for only 30% of the benzene-soluble chloro-compound.

Diphenoxy-6 : 6′-*azoquinoxaline*.—Dichloro-6 : 6′-azoquinoxaline (0·1 g. crude) was heated with a solution of potassium hydroxide (0·05 g.) in phenol (0·5 g.) for ¾ hr. on a steam-bath, and the mixture was cooled somewhat and poured into 2N-sodium hydroxide (15 c.c.). The orange solid (0·17 g.) had m. p. 205—220° and on its being heated with phenol–ethanol a small fraction (0·025 g.), m. p. 275—285°, remained undissolved. Further solid (0·025 g.), m. p. 230—240°, separated on cooling. Addition of more ethanol precipitated a third fraction (0·03 g.), m. p. 180—210°. None of these fractions was crystalline.

In another experiment the crude product was chromatographed on Type "H" alumina. The only crystalline material obtained was a little of the α-dichloro-compound.

4-*Acetamido*-3-*nitroazobenzene*.—(*a*) Solutions in acetic acid of 2-nitro-4-nitrosoacetanilide (0·18 g. in 2 c.c.) and aniline (0·1 c.c. in 1 c.c.) were mixed and set aside overnight. Addition of water precipitated 4-*acetamido*-3-*nitroazobenzene* (0·23 g.) which crystallised from aqueous methanol in golden-yellow needles, m. p. 143—145° (Found: C, 58·9; H, 4·1; N, 19·7. $C_{14}H_{12}O_3N_4$ requires C, 59·1; H, 4·3; N, 19·7%).

(*b*) Warm solutions in acetic acid of 4-amino-2-nitroacetanilide (19 g. in 125 c.c.) and nitrosobenzene (15 g. in 125 c.c.) were mixed and set aside overnight. Addition of water precipitated the same compound (25 g.) as in (*a*).

4-*Amino*-3-*nitroazobenzene*.—The foregoing acetamido-compound (24·9 g.) was refluxed with ethanol (500 c.c.), and concentrated hydrochloric acid (250 c.c.) was added. The crystals which separated quickly from a clear solution were filtered off when cold, combined with a second crop obtained by dilution, and recrystallised from acetic acid (1·1 l., 73%), to provide orange-red needles (19·8 g.), m. p. 171—173° or 172—174° (from aqueous ethanol), of 4-*amino*-3-*nitroazobenzene* (Found: C, 59·8; H, 3·9; N, 23·1. $C_{12}H_{10}O_2N_4$ requires C, 59·5; H, 4·2; N, 23·1%).

3 : 4-*Diaminoazobenzene*.—The nitroamine (5 g.), ethanol (100 c.c.), and a 19% solution of sodium hydrogen sulphide (20 c.c.) were heated at 50° for 30 min. and the dark red solution was diluted with water (120 c.c.). Orange needles (3·68 g.; m. p. 125—136°) were collected from the cold mixture, and a second crop (0·60 g., m. p. 135—138°) was obtained by addition of water (250 c.c.) to the filtrate. The first crop yielded on recrystallisation (carbon) from a mixture of ethanol (50 c.c.) and water (35 c.c.) orange-red needles (0·66 g.) of the starting material, m. p. and mixed m. p. 172—173°. The second crop was recrystallised (carbon) from the aqueous-alcoholic mother-liquor with added water (75 c.c.) and ethanol (20 c.c.), to provide orange-yellow needles of 3 : 4-*diaminoazobenzene* (3·28 g.), m. p. 135—138° raised to 137·5—139·5° on recrystallisation from benzene–light petroleum (b. p. 60—80°) Found: C, 67·4; H, 5·7; N, 26·7. $C_{12}H_{12}N_4$ requires C, 67·9; H, 5·7; N, 26·4%).

4 : 4′-*Diamino*-3 : 3′-*dinitroazoxybenzene*.—The diacetamido-compound (0·3 g.) was refluxed

for 90 min. with acetic acid (10 c.c.) and concentrated hydrochloric acid (10 c.c.). The bulky orange precipitate [0·24 g.; m. p. 320—325° [decomp.)] was collected cold and recrystallisation from phenol-ethanol gave the *diamino*-derivative, m. p. 328—330° (decomp.), as orange-red tabular needles (Found: C, 45·9; H, 3·4; N, 26·9. $C_{12}H_{10}O_5N_6$ requires C, 45·3; H, 3·2; N, 26·4%).

**3 : 3′ : 4 : 4′-*Tetra-aminoazoxybenzene.*—4 : 4′-Diamino-3 : 3′-dinitroazoxybenzene (0·16 g.), butanol (10 c.c.), ethanol (10 c.c.), and a 19% solution of sodium hydrogen sulphide (3·5 c.c.) were heated together on a steam-bath for 1 hr. and the mixture then cooled, carefully acidified with concentrated hydrochloric acid, and clarified. More hydrochloric acid was added to the filtrate, and the amorphous black hydrochloride was collected, dissolved in water, and basified. The *tetra-amino*-compound (0·05 g.) crystallised from water as golden tabular needles, m. p. 231—233° (decomp.) (Found: C, 56·4; H, 5·6; N, 33·2. $C_{12}H_{14}ON_6$ requires C, 55·8; H, 5·5; N, 32·6%).

3-*Nitroazobenzene.*—(*a*) Warm solutions of *m*-nitroaniline (1 g.) and nitrosobenzene (1·3 g.) in acetic acid (5 c.c. each) were mixed and set aside overnight. The mixture was diluted and the product (1·37 g.), m. p. 94°, recrystallised (charcoal) from aqueous ethanol to provide 3-nitroazobenzene, m. p. 95—97° (Bamberger and Hübner, *loc. cit.*, give m. p. 95—96°).

(*b*) 4-Amino-3-nitroazobenzene (0·5 g.) was diazotised at 0° in a mixture of concentrated sulphuric acid (15 c.c.) and water (15 c.c.) with a 20% solution of sodium nitrite (1·2 c.c.). Hypophosphorous acid (40 c.c. of a 30% solution) was added at 0° and the mixture set aside overnight. The precipitate was recrystallised successively from aqueous ethanol and aqueous acetic acid, and the product (0·32 g.), m. p. 86—94°, chromatographed in benzene–light petroleum (b. p. 60—80°) (2 : 1), to provide golden needles (0·25 g.) of 3-nitroazobenzene, m. p. and mixed m. p. with (*a*) 96—98°.

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Ultra-violet Absorption Spectra of 9-Substituted Fluorenes.

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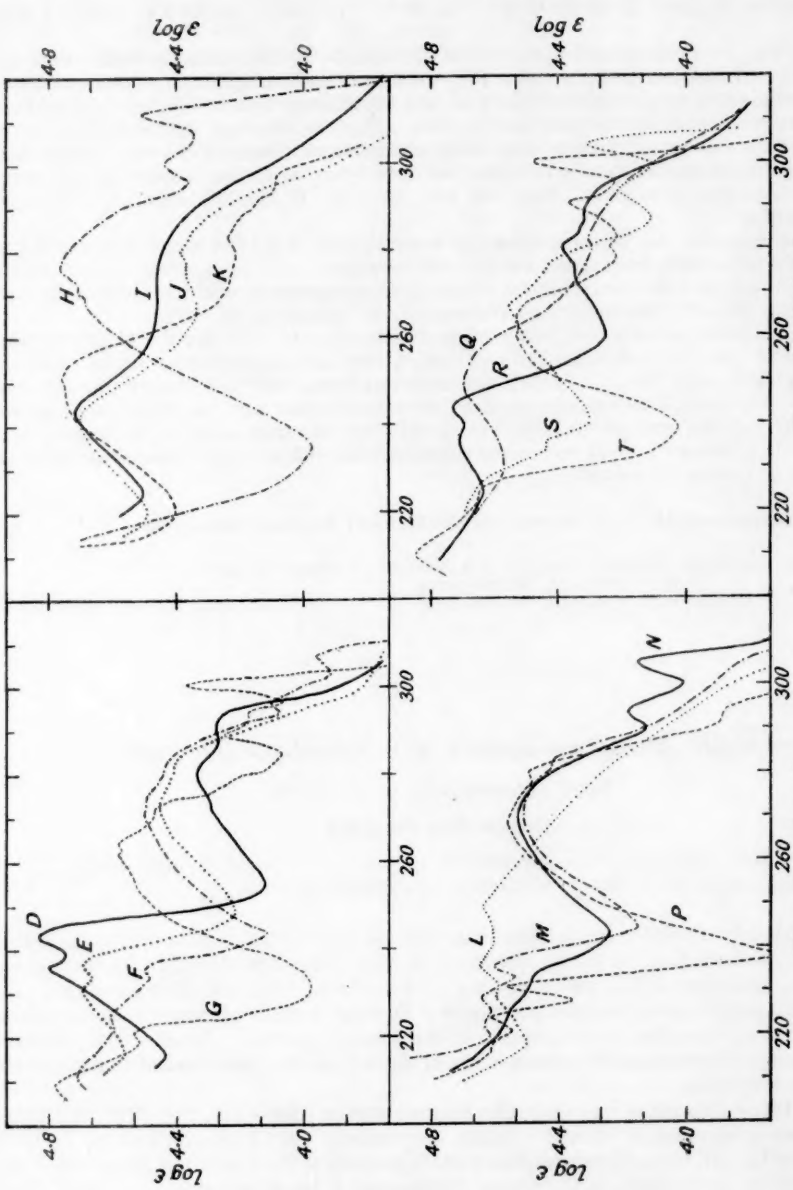
Some electronegative substituents in the 9-position of fluorene cause significant changes in the ultra-violet absorption spectrum.

DATA previously available in the literature seemed to indicate that simple substituents attached by a single bond at the 9-position of fluorene cause little change in the ultra-violet absorption, and thus Miller and Wagner (*J. Org. Chem.*, 1951, **16**, 279) conclude: "it appears that simple substituents in position-9 of fluorene, and the presence of an α,β-double bond, do not greatly alter the absorption of the fluorene system." Results now presented show that some electronegative substituents in the 9-position cause marked changes in the absorption spectrum.

If the three absorption regions in the fluorene system (200—225, 245—275, and 285—305 mμ) are designated A, B, and C bands, respectively (cf. Clemo and Felton, *J.*, 1952, 1658) it will be seen from the figures that a chlorine atom in the 9-position moves the A and B bands by *ca.* 12 mμ towards the visible, flattens the B band, and eliminates the C band. Bromine produces a bathochromic shift of *ca.* 25 mμ (in this case the two maxima of the A band have merged), and the intensity of the B band is further depressed. The shift is even greater for iodine, and the B band becomes only a plateau (partly because of broadening of the A band). Introduction of a second chlorine or bromine atom in the 9-position causes further changes of the same kind, and halogens have a similar effect when they replace



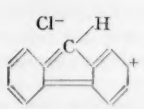
D, 9 : 9-Dichlorofluorene; *E*, 9-chlorofluorene; *F*, 9-ethoxyfluorene; *G*, fluorene; *H*, 2 : 7-dibromofluorene (in EtOH); *I*, 9-iodofluorene; *J*, 9-bromofluorene; *K*, 9 : 9-dibromofluorene; *L*, 9-bromo-9-nitrofluorene; *M*, 9-azidofluorene (in EtOH); *N*, 9-aminofluorene (in EtOH); *P*, 9-aminofluorene (in acidified ethanol); *Q*, 9-bromo-9-phenylfluorene; *R*, 9-chloro-9-phenylfluorene; *S*, 9-phenylfluorene; *T*, 9-trimethylsilylfluorene.

hydrogen in the 9-positions of 9-trimethylsilyl- and 9-phenyl-fluorene and of di-9-fluorenyldimethylsilane. Related, but smaller, changes were noticed when halogen replaced hydrogen in what was believed to be the quaternary carbon position of 9-phenyl-1 : 2-3 : 4-7 : 8-tribenzofluorene (R. N. Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2025). The changes in spectrum produced by one or two halogen atoms in the 9-position are markedly greater than those produced by halogens in the most sensitive aromatic positions of fluorene, where they cause small bathochromic shifts with very little change in shape of the absorption curve.

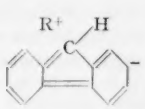
Other electronegative substituents in the 9-position cause similar changes in the absorption spectrum of fluorene, and the order of effectiveness of single substituents in causing bathochromic shifts, accompanied by flattening of the B band and suppression of the C band, is $H < NH_2,OEt < N_3,Cl < Br < I$. The most marked change in shape of the curve is found with 9-bromo-9-nitrofluorene, in which the B band appears to have been submerged and the C band eliminated.

There are distinct differences between the absorption curves of 9-aminofluorene in neutral and acidified ethanol, respectively, and the absorption of the ammonium-ion compound is somewhat similar to that of 9-azido- and 9-chloro-fluorene. Since the positive nitrogen atom does not have a greater effect than the halogens on the absorption, electron-withdrawal by an inductive mechanism seems not to be a major factor in the influence of 9-substituents on the spectrum of fluorene.

Detailed explanation of the spectral changes described must await assignment of the bands of the fluorene spectrum, but we suggest that the effects may originate in negative hyperconjugation (cf. Hughes, Ingold, and de la Mare, *J.*, 1948, 17; Braude and Coles, *J.*, 1951, 2085; Armitage and Whiting, *J.*, 1952, 2005), involving contributions to an excited state of structures such as (I). Resonance stabilisation of the excited state relative to the ground state would account for the bathochromic shifts. and the polarizability of the C–X bonds would explain the order of effectiveness of various groups X given above. In agreement with this, trimethylsilyl, methyl, and phenyl groups in the 9-position cause slight bathochromic shifts below 250 mμ, but little change in the position and shape of the B and C bands. In these cases hyperconjugation would presumably lead to structures of type (II) (R = Me_3Si, Me, or Ph) similar to those expected to contribute to the structure of fluorene itself (R = H).



(I)



(II)

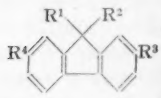
In view of the ease with which halogen may be introduced into the 9-position of fluorene and analogous positions of more complex compounds, the spectral effects described could help in determinations of structure.

Experimental

Materials.—The following fluorene derivatives were prepared by established methods: 9-bromo-, m. p. 104·5° (from acetone) (Wittig and Felletschin, *Annalen*, 1944, **555**, 133); 9-iodo- (from light petroleum), m. p. (rapid heating) 107—108°, with decomp. at 125° (Wanscheidt, *Ber.*, 1926, **59**, 2092); 9-chloro-, m. p. 91·5° (from glacial acetic acid containing hydrochloric acid) (Staudinger, *Ber.*, 1906, **39**, 3060); 9-azido-, m. p. 44° (from aqueous ethanol) [Arcus and Mesley's method (*J.*, 1953, **178**) was modified by using 9-bromo- in place of 9-chloro-fluorene and boiling for 2 hr.]; 9-amino-, m. p. 62° (from light petroleum) (Ingold and Wilson, *J.*, 1933, 1493); 9 : 9-dibromo-, m. p. 118° (from *cyclo*hexane) [Wittig and Vidal's method (*Chem. Ber.*, 1948, **81**, 368) was modified by illumination with a 150-w lamp during reflux for 6 hr.]; 9-bromo-9-phenyl-, m. p. 99° (from light petroleum) (Buu-Hoï, *Annalen*, 1944, **556**, 1); 9-chloro-9-phenyl-, m. p. 78° (from light petroleum) (Staudinger, *loc. cit.*); 9 : 9-dichloro-, m. p. 103° (from ether) (Schmidt and Wagner, *Ber.*, 1910, **43**, 1796); 9-bromo-2-nitro-, m. p. 143·5° (from ethanol) (Anantakrishman and Hughes, *J.*, 1935, 1607); 9-bromo-9-nitro-, m. p. 108° (decomp.) (from

ethanol) (Wislicenus and Waldmüller, *Ber.*, 1908, **41**, 3334); 2-nitro-, m. p. 156° (from ethanol) ("Org. Syntheses," Chapman and Hall, London, Coll. Vol. II, p. 447).

Methods of preparation of other compounds will be described in a separate communication.



Spectra.—Solutions in *n*-hexane or (where indicated) 95% ethanol were examined with a Unicam S.P. 500 Spectrophotometer, usually not below 215 mμ.

Absorption data tabulated refer to fluorene derivatives not included in the diagrams. The letter under "Shape" indicates which curve in the diagram the absorption resembles.

R¹	R²	R³	R⁴	$\lambda_{max.}$ (mμ) with log ε in parentheses					Shape
[a] Me_3Si	Me_3Si	H	H	255 * (4·10)	264 (4·19)	291·5 (4·04)	300 (4·02)	—	*T*
Me	Me_3Si	H	H	262 (4·16)	267 (4·18)	290·5 (3·95)	301 (4·07)	—	*T*
OEt	Me_3Si	H	H	213·5 (4·26)	273 (4·14)	282 * (4·01)	293·5 (3·81)	305 (3·82)	*F*
[b] Br	Me_3Si	H	H	245 (4·40)	279 (4·00)	—	—	—	*J*
Cl	Me_3Si	H	H	223 * (4·41)	232 (4·40)	238·5 (4·39)	275 (4·08)	284 * (4·02)	*E*
[ab] H	Me_3Si	Br	H	270·5 (4·32)	289 * (3·96)	294 (4·04)	299·5 (4·05)	305·5 (4·11)	*H*
[a] H	Me_3Si	Br	Br	272 * (4·39)	276 (4·42)	299·5 (4·17)	302 * (4·14)	311 (4·35)	*H*
[b] H	H	Br	H	270 (4·39)	295 (3·90)	298 * (3·88)	306 (3·98)	—	*H*
[c] —	—	—	—	227 * (4·69)	261 (4·49)	265·5 (4·49)	278 (4·09)	290 (4·24)	*T*
[d] —	—	—	—	245·5 (4·60)	280 * (4·14)	—	—	—	*J*
H	H	NO_2	H	233 (4·00)	331 (4·26)	—	—	—	—
Br	H	NO_2	H	225 (4·35)	256 (4·01)	263·5 * (3·95)	268 (3·96)	322 (4·23)	—
[b] Br	H	NO_2	H	225·5 (4·30)	271 * (3·81)	274 * (3·82)	330 (4·19)	—	—
Br	Me_3Si	NO_2	H	229 (4·23)	262·5 (3·94)	316 * (4·19)	326·5 (4·23)	—	—
[b] H	H	NO_2	NO_2	~247 (3·90)	331 (4·43)	—	—	—	—

* Inflexion. [a] Not studied below 230 mμ. [b] In ethanol. [c] Di-(9-bromo-9-fluorenyl)dimethylsilane; there is also a band at 300 mμ (log ε 4·39). [d] Di-9-fluorenyldimethylsilane.

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[*Received, February 3rd*, 1954.]

Interaction of Carboxylic Acids with Phosphorus Trichloride, or Butyl Phosphorodichloridite, or the Chloridite in the Absence, and in the Presence of Pyridine.

By J. A. CADE and W. GERRARD.

[Reprint Order No. 5095.]

With acids such as acetic acid there was no evidence that chlorine attached to phosphorus in the trichloride or the phosphorochloridites could be replaced by an acyloxy-group by a primary reaction either in the absence or in the presence of pyridine, as it can be by an alkoxy-group. The primary reaction was the formation of acyl chloride. By a secondary reaction, and this only in the case of butyl phosphorodichloridite in the presence of pyridine, an acyl phosphite was obtained. However, benzoic acid, the trichloride, and pyridine immediately gave tribenzoyl phosphite on being mixed.

Correlation with the corresponding thionyl chloride systems is mentioned.

LITTLE has been reported on the mechanism of the interaction of carboxylic acids and phosphorus trichloride, although the yields of acyl chlorides have been discussed (cf. Clark and Bell, *Trans. Roy. Soc. Canada*, 1933, **27**, III, 97; Bauer, *Oil and Soap*, 1946, **23**, 1). In many text-books the equation (1) is given; but in others equation (2) is favoured in order to allow for the formation of hydrogen chloride, which has also been attributed to reaction (3) (Lucas and Pressman, "Principles and Practice in Organic Chemistry," Wiley, New York, 1949, p. 267). Brooks (*J. Amer. Chem. Soc.*, 1912, **34**, 492) concluded that (1) was

(1) $3R{\cdot}CO_2H + PCl_3 \longrightarrow 3R{\cdot}COCl + P(OH)_3$

(2) $3R{\cdot}CO_2H + 2PCl_3 \longrightarrow 3R{\cdot}COCl + P_2O_3 + 3HCl$

(3) $CH_3{\cdot}CO_2H + PCl_3 \longrightarrow CH_3{\cdot}CO_2{\cdot}PCl_2 + HCl$, etc.

correct for the interaction of the acid and trichloride, but the reduced yield of acyl chloride and the evolution of hydrogen chloride were ascribed to reactions (4) and (5):

(4) $CH_3{\cdot}COCl + CH_3{\cdot}CO_2H \longrightarrow (CH_3{\cdot}CO)_2O + HCl$

(5) $CH_3{\cdot}COCl + P(OH)_3 \longrightarrow P(OH)_2{\cdot}O{\cdot}CO{\cdot}CH_3 + HCl$

The main point to be established is whether chlorine attached to tervalent phosphorus can be replaced by an acyloxy-group, and from experience with the corresponding alcohol systems, the reaction with dibutyl phosphorochloridite $PCl(OBu^n)_2$ in the presence of pyridine should be a crucial test (Gerrard, *J.*, 1940, 1464; Gerrard, Isaacs, Machell, Smith, and Wyvill, *J.*, 1953, 1920). Addition of the chloridite (1 mol.) to a solution of acetic acid (2 mols.) and pyridine (1 mol.) in pentane at $-10°$ immediately afforded acetic anhydride (97% yield), dibutyl hydrogen phosphite (92%), and base hydrochloride. This result is considered to be due to the direct formation of acetyl chloride (1 mol.) and hydrogen phosphite, followed by interaction of the former and acetic acid (1 mol.) facilitated by the base (1 mol.) (Gerrard and Thrush, *J.*, 1952, 741; 1953, 2117). Only 1 mol. of the base was required, because, even if it took part in the first reaction, its availability for the second one would not be reduced by the neutral hydrogen phosphite. In the absence of pyridine, equimolecular proportions of chloridite and acid readily gave acetyl chloride (84%) and the hydrogen phosphite at 20°. But for the first result, this could be ascribed to the formation of acetyl dibutyl phosphite and the deacylation of it by hydrogen chloride as in the alcohol system: $PCl(OR)_2 + ROH \longrightarrow HCl + P(OR)_3 \longrightarrow O{:}PH(OR)_2 + RCl$. The other aliphatic acids examined behaved as acetic acid did.

Complications arose when butyl phosphorodichloridite was used. The dichloridite (1 mol.), acetic acid (2 mols.), and base (2 mols.) gave at 20° base hydrochloride, acetic anhydride (29%), and diacetyl butyl phosphite (44·6%). Butyl di*iso*butyryl phosphite and the dipropionyl compound were also obtained in a similar way. We believe that the acyl chloride was formed by a direct process as before, and that the other product, $PCl(OH)\cdot OR$, decomposed to base hydrochloride and butyl metaphosphite, which with the anhydride formed diacyl butyl phosphite. Some support for this tentative suggestion is given by the fact that phosphorus trichloride and acid did not give acyl phosphite in the presence of base. About the intermediate phosphorus compounds mentioned, nothing appears to be known. We have not succeeded in preparing butyl metaphosphite, but by hydrolysing the dichloridite with the correct amount of water to form the compound $PCl(OH)\cdot OR$ in the presence of pyridine and acetic anhydride, we obtained base hydrochloride in almost theoretical yield and diacetyl butyl phosphite in 22·5% yield.

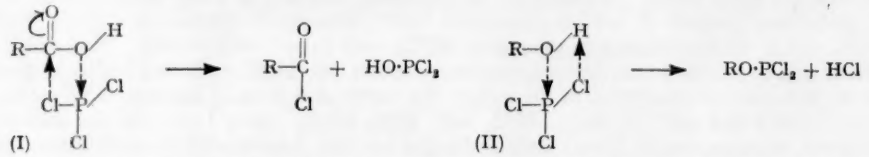
In the phosphorus trichloride–acid system we could find no evidence of R·CO·O–P bond formation, either in the absence or in the presence of base. We infer that two of the chlorine atoms readily cause direct formation of acyl chloride, equation (6) and (7), but

$$(6)\quad R\cdot CO_2H + PCl_3 \longrightarrow R\cdot COCl + PCl_2\cdot OH$$
$$(7)\quad R\cdot CO_2H + PCl_2\cdot OH \longrightarrow R\cdot COCl + PCl(OH)_2$$

there can be complications over the third atom. From the yields of acyl chloride we conclude that the compound $PCl(OH)_2$ can continue to form acyl chloride, but some of it is degraded to hydrogen chloride and metaphosphorous acid. From the acid (3 mols.) and trichloride (1 mol.) at temperatures $< 20°$ the yields of acyl chloride were acetyl 69, propionyl 72, *iso*valeryl 70%; and the residues contained from 36·4 to 42% of phosphorus [Calc. for $P(OH)_3$: P, 37·8%]. The loss of available chlorine can be compensated by providing more trichloride, but more than a small increase is a disadvantage in the examples of the lower members, because unchanged reagent interferes with purification of the acyl chloride. Clark and Bell (*loc. cit.*) do not mention having tried proportions other than trichloride (1·8 mols.) and acid (3 mols.) with which they obtained acetyl (79%), *n*-butyryl (68%), and *iso*hexanoyl (55%) chloride. For the preparation of chlorides of higher fatty acids (*e.g.*, stearic acid), Bauer (*loc. cit.*) used 1 mol. of trichloride to 1 of acid, 0·4 mol. of the former giving lower yields.

In the presence of pyridine a complication arose probably owing to the association of the base with the compound $PCl(OH)_2$. With ether or pentane as solvent there was a coprecipitation of base and reactive chlorine, so that with the reagents in the ratio $PCl_3 : 3CH_3\cdot CO_2H : 3C_5H_5N$, the yield of acetic anhydride was only 44%. To keep the chlorine available for formation of acyl chloride, and to ensure that there was enough pyridine to convert the acyl chloride into anhydride, we used chloroform as solvent and varied the proportions of reagents. With propionic acid (6 mols.), pyridine (4 mols.), and tri-

chloride (1 mol.), the yield of anhydride was 92%. This result is in accord with the view that acyl chloride is formed by a direct process and then forms anhydride as described. Provisionally we depict this direct process as involving a four-centre transition state (I) but with a different orientation of reactive centres from that in the alcohol sytsem (II).



It is remarkable that benzoic acid (3 mols.), trichloride (1 mol.), and pyridine (3 mols.) gave base hydrochloride and tribenzoyl phosphite, obtained as a white solid. On the other hand, the acid reacted with thionyl chloride in the presence of pyridine as did acetic acid (Gerrard and Thrush, *loc. cit.*). Only one chlorine atom in thionyl chloride is available for formation of acyl chloride, the reaction apparently being similar to (I), the other product, SOCl·OH, decomposing to sulphur dioxide and hydrogen chloride. In the presence of pyridine, acyl chloride is formed in the same way; but the base and the compound SOCl·OH are both precipitated from ether or pentane. Consequently, 2 mols. of base are required for the conversion of 2 mols. of acid into anhydride by 1 mol. of thionyl chloride. Not even when butyl chlorosulphinate was used in the presence of pyridine was there any evidence of the formation of an acyl sulphite.

Experimental

Interaction of Acid (2 Mols.) with Dibutyl Phosphorochloridite (1 Mol.) in the Presence of Pyridine (1 Mol.).—The chloridite (10·63 g.) in pentane (25 c.c.) was added dropwise to a shaken solution of acetic acid (6·0 g.) and base (3·95 g.) in pentane (50 c.c.) at −10°; base hydrochloride (5·35 g.) was formed immediately. The filtrate gave acetic anhydride (4·95 g., 97%), b. p. 40—41°/11 mm. (Found: equiv., 51·8. Calc.: equiv., 51·0), dibutyl hydrogen phosphite (8·9 g., 92%), b. p. 130—133°/19 mm., n_D^{20} 1·4220 (Found: P, 15·8. Calc. for $C_8H_{19}O_3P$: P, 16·0%), and an undistillable glassy residue (1·0 g.) containing phosphorus (13·2%).

With *iso*butyric acid (8·8 g.), base hydrochloride (5·15 g.), *iso*butyric anhydride (7·0 g., 88·5%), b. p. 70—75°/11 mm. (Found: equiv., 79·7. Calc.: equiv., 79·0), a mixed fraction (0·5 g.), b. p. 105—120°/11 mm., dibutyl hydrogen phosphite (8·65 g., 89%), b. p. 125—130°/11 mm., n_D^{20} 1·4225 (Found: P, 15·5%), and an undistillable residue (1·4 g.) (Found: P, 12·0%) were obtained.

With *n*-heptanoic acid (12·0 g.), base hydrochloride (5·5 g.), a distillate (18·9 g.) with a long boiling range, and a residue (1·6 g.) were obtained. The distillate provided fractions from b. p. 70°/0·4 mm., n_D^{20} 1·4242 (Found: P, 12·0%), to b. p. 114°/0·4 mm., n_D^{20} 1·4331 (Found: P, 0·9%). It was not possible to separate dibutyl hydrogen phosphite, n_D^{20} 1·4215, and heptanoic anhydride, n_D^{20} 1·4340. All precipitates were good specimens of pyridine hydrochloride.

Benzoic acid (12·2 g.) behaved differently. Base hydrochloride weighed 3·8 g., and no hydrogen phosphite could be isolated. The distillates, b. p. 145—265°/0·005 mm., contained phosphorus, and on standing gave benzoic acid and benzoic anhydride. When benzoic acid (6·1 g., 1 mol.) in ether (total, 125 c.c.) was used, base hydrochloride weighed 5·1 g., but again the hydrogen phosphite could not be isolated. The behaviour on distillation indicated the presence of benzoyl dibutyl phosphite which was undergoing some decomposition to benzoic anhydride and polymerised material containing phosphorus. One fraction had b. p. 126—140°/0·01 mm., n_D^{20} 1·5032 (Found: P, 8·5%).

Acetic Acid and Dibutyl Phosphorochloridite.—The chloridite (10·63 g., 1 mol.) was quickly mixed with acetic acid (3·0 g., 1 mol.) in a flask which was immediately connected to an absorption tube (KOH) and shaken mechanically for 1 hr. at 20°. The absorption tube was replaced by a trap at −80°, followed by another absorption tube (KOH), and volatile matter was removed from the reaction vessel at 20°/1·0 mm. The two tubes contained but a trace of chloride ion. Trap contents (3·8 g.) gave acetyl chloride (3·3 g., 84%), b. p. 50—52° (Found: Cl, 46·3. Calc. for C_2H_3OCl: Cl, 45·2%). Residue (9·75 g.) in the reaction flask gave mainly dibutyl hydrogen phosphite, b. p. 91—93°/0·65 mm., n_D^{20} 1·4247 (Found: P, 15·0%), but it was not possible to free it completely from a chlorine compound by distillation.

Interaction of Butyl Phosphorodichloridite (1 *Mol.*) *with Acid* (2 *Mols.*) *and Pyridine* (2 *Mols.*).—The dichloridite (17·6 g.) in pentane (50 c.c.) was added dropwise to acetic acid (12·0 g.) and pyridine (15·8 g.) in pentane (250 c.c.) at −10°. A good specimen of base hydrochloride (23·25 g.) was formed during the mixing. From the filtrate, volatile matter was removed at 20°/0·1 mm. and collected at −80°, and from it acetic anhydride (3·0 g., 29·4%), b. p. 132—135°, was obtained. The primary residue (20·8 g.) afforded a fraction (0·95 g.), b. p. 75°/0·1 mm., n_D^{20} 1·4291, *diacetyl butyl phosphite* (9·9 g., 44·6%), b. p. 70—73°/0·07 mm., n_D^{20} 1·4261 (Found: C, 43·9; H, 7·0; P, 14·1. $C_8H_{15}O_5P$ requires C, 43·2; H, 6·75; P, 13·9%), a fraction (1·65 g.), b. p. 80—110°/0·1 mm. (decomp.), and a residue (4·3 g.) (Found: P, 23·3%). After being kept at 15° for 14 days, the acetyl phosphite gave a range of fractions, the main fraction (4·8 g.) having b. p. 76—79°/0·4 mm., n_D^{20} 1·4352 (Found: P, 14·5%). In a trap at −80° placed between the receiver and the pump trap, acetic anhydride (0·8 g.) was collected.

Similarly from *iso*butyric acid (8·95 g., 2 mols.) and pyridine (7·9 g., 2 mols.), base hydrochloride (11·2 g.), *iso*butyric anhydride (3·9 g., 48·5%), b. p. 170—176° (Found: equiv., 80·3. Calc.: equiv., 79·0), n-*butyl diisobutyryl phosphite* (4·6 g., 33%), b. p. 80—84°/0·07 mm., n_D^{20} 1·4279 (Found: C, 51·0; H, 8·0; P, 11·0. $C_{12}H_{23}O_5P$ requires C, 51·8; H, 8·3; P, 11·15%), a fraction (1·05 g.), b. p. 114—118°/0·4 mm., n_D^{20} 1·4332, and an undistillable residue (2·25 g.) (Found: P, 18·2%) were obtained.

Similarly, propionic acid (7·4 g., 2 mols.) afforded base hydrochloride (11·5 g.), propionic anhydride (2·3 g., 35·4%), b. p. 152—154° (Found: equiv., 65·5. Calc.: equiv., 65·0), *butyl dipropionyl phosphite* (6·3 g., 50·4%), b. p. 84—88°/0·01 mm., n_D^{20} 1·4377 (Found: P, 12·3. $C_{10}H_{19}O_5P$ requires P, 12·4%), and an undistillable residue (2·2 g.) (Found: P, 15·1%).

With the intention of forming butyl metaphosphite (believed to be responsible for the diacyl phosphite) in a different way, the dichloridite (8·8 g., 1 mol.) was added rapidly to acetic anhydride (20·5 g.) at −10°. A mixture of pyridine (7·9 g., 2 mols.) and water (0·9 c.c., 1 mol.) was then added. After 1 hr., ether (200 c.c.) was added. The insoluble matter (11·0 g.) was a good specimen of base hydrochloride. Evaporation at 20°/0·1 mm. afforded ether, acetic anhydride (17·3 g.), and a residue which gave diacetyl butyl phosphite (2·5 g., 22·5%), b. p. 67—70°/0·09 mm., n_D^{20} 1·4255 (Found: P, 14·1%).

Acid and Phosphorus Trichloride.—The trichloride (11·46 g., 1 mol.) was added to acetic acid (15 g., 3 mols.) at 20°, and the mixture was shaken for 2 hr. Two layers separated immediately, and only 0·003 g.-ion of chlorine was held in the alkali trap which followed the trap kept at −80°. Volatile matter was removed at 20°/15 mm. (1 hr.), and after being warmed to 50°/0·05 mm. during 1 hr. the residue weighed 6·0 g. (Found: P, 42·0. Calc. for H_3O_3P: P, 37·8%). The contents of the cold trap were distilled, a cold trap, followed by the existing alkali trap, being attached to the receiver. Hydrogen chloride (total, 0·48 mol.), acetyl chloride (13·5 g., 69%), b. p. 50—52° (Found: Cl, 46·0. Calc.: Cl, 45·2%), and acetic acid contaminated with hydrogen chloride were isolated. In another experiment acetyl chloride (70% yield), b. p. 50—52°, d_4^{20} 1·105 (Found: Cl, 45·1%), and a residue (Found: P, 40·8%) were obtained.

Similarly, propionic acid (18·5 g., 3 mols.) and trichloride (1 mol.) afforded hydrogen chloride (0·62 mol.) and acyl chloride (16·7 g., 72%), b. p. 75—77° (Found: Cl, 39·2. Calc. for C_3H_5OCl: Cl, 38·4%). *iso*Valeric acid (10·2 g.) afforded the chloride (8·4 g., 70%), b. p. 114—115° (Found: Cl, 29·5. Calc. for C_5H_9OCl: Cl, 29·5%), and a residue (6·62 g.) (Found: P, 36·4%). A mixture of unchanged acid and some anhydride accounting for about 10% of total acid was obtained. During the reaction at 20° the hydrogen chloride evolved was only 0·04 mol.

Interaction of Propionic Acid with Phosphorus Trichloride in Presence of Pyridine.—The trichloride (11·46 g., 1 mol.) in pentane (50 c.c.) was added dropwise to a solution of the acid (37·35 g., 6 mols.) and pyridine (39·5 g., 6 mols.) in pentane (200 c.c.) at −10°. The precipitate (33·0 g.) (Found: $Cl : C_5H_5N : P = 2·91 : 2·76 : 0·63$) was formed immediately, and from the filtrate volatile matter was removed at 20°/15 mm. The residue (52·0 g.) gave impure acid (6·7%), b. p. 135—140° (Found: equiv., 75·2. Calc. for $C_3H_6O_2$: equiv., 74·0), a mixture of acid and anhydride (1·5 g.), b. p. 140—158°, propionic anhydride (24·0 g., 73%), b. p. 158—160°, and a residue which at 0·1 mm. gave a further 12% of anhydride. The final residue weighed 3·2 g. (0·03 mol.) (Found: P, 28·0%).

As the pyridine compounds in this system are soluble in chloroform, reactions were carried out in this solvent. The yield of anhydride never exceeded 88%, some acid was always recovered and no evidence of the formation of acyl phosphites could be secured. It appeared that pyridine was not urgently required for the formation of the intermediate acyl chloride, but would probably have the effect of reducing the reactivity of the postulated intermediate $PCl(OH)_2$. We therefore reduced the proportion of base to 3 mols; but this was too drastic, for the phos-

phorous acid then withheld pyridine from the anhydride reaction. The yield of anhydride was 68%, and some acid and acyl chloride were present. The optimum amount of base was about 4 mols. Trichloride (11·46 g., 1 mol.) was added to the acid (6 mols.) and pyridine (4 mols.) in chloroform (250 c.c.). Removal of volatile matter at 20° (low pressure) gave a residue (43 g.) (Found: Cl : C_5H_5N : P = 2·72 : 3·24 : 0·99) which contained all the phosphorus. The trapped distillate afforded anhydride (30·0 g., 92%), b. p. 158—162° (Found: equiv., 66·0. Calc. for $C_6H_{10}O_3$: equiv., 65·0), and a mixture of acid and anhydride.

Interaction of Benzoic Acid and Phosphorus Trichloride in the Presence of Pyridine.—Benzene proved to be a better solvent than ether. The trichloride (2·3 g., 1 mol.) in benzene (5 c.c.) was added dropwise to a solution of benzoic acid (6·1 g., 3 mols.) and pyridine (3·95 g., 3 mols.) in benzene (30 c.c.) at 0°. A good specimen of base hydrochloride (5·65 g., 98%) (Found: Cl, 30·2; C_5H_5N, 67·1. Calc. for C_5H_6NCl: Cl, 30·7; C_5H_5N, 68·4%) was immediately formed, and the filtrate gave *tribenzoyl phosphite* (6·32 g., 96%), m. p. 93—95° (Found: P, 7·8. $C_{21}H_{15}O_6P$ requires P, 7·9%). This compound (3·7 g.) gave on distillation at 0·1 mm. benzoic anhydride (1·1 g.), b. p. 40—41°/0·1 mm. (Found: equiv., 112·6. Calc.: equiv., 113·0), and a glassy residue (2·0 g.) (Found: P, 13·2%).

Butyl phosphorodichloridite (8·8 g., 1 mol.) in benzene (50 c.c.) was added to a solution of benzoic acid (12·2 g., 2 mols.) and pyridine (7·9 g., 2 mols.) in benzene (300 c.c.) at 20°. A good specimen of base hydrochloride (10·4 g.) (Found: Cl, 30·4; C_5H_5N, 67·6%) was immediately formed. Evaporation of the solvent afforded a residue (19·1 g.) which could be neither crystallised nor distilled. It was thoroughly degassed at 40°/0·05 mm. (Found: P, 8·4. Calc. for $C_{18}H_{19}O_5P$: P, 9·0%).

Materials.—All solvents were dried, and reagents were distilled just before use. Butyl phosphorodichloridite was prepared as described by Gerrard (*loc. cit.*) and dibutyl phosphorochloridite as described by Gerrard *et al.* (*J.*, 1953, 1920).

Dr. A. M. Thrush prepared the tribenzoyl phosphite.

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αβ-*Unsaturated Aldehydes and Related Compounds. Part IV.** *The Homolytic Addition of Carbon Tetrachloride to Acraldehyde and its Acetals.*

By R. H. HALL and D. I. H. JACOBS.

[Reprint Order No. 5003.]

The homolytic addition of carbon tetrachloride to acraldehyde and to two of its acetals has been investigated. The free aldehyde gave no useful results, but the diethyl acetal under the influence of ultra-violet irradiation gave a poor yield of αγγγ-tetrachlorobutaldehyde diethyl acetal; a similar result was obtained with a cyclic acetal of acraldehyde, *viz.*, 4-methyl-2-vinyl-1 : 3-dioxan. In both cases higher-boiling compounds derived from 1 mol. of tetrahalide and 2 mols. of the acetal were also obtained.

THE homolytic addition of polyhalogenomethanes to olefinic compounds under the influence of free-radical chain initiators of the diacyl peroxide type, or of ultra-violet irradiation, has been extensively investigated by Kharasch and his co-workers (*Science*, 1945, **102**, 128; *J. Amer. Chem. Soc.*, 1945, **67**, 1626, 1864; 1946, **68**, 154; 1947, **69**, 1100, 1105; *J. Org. Chem.*, 1948, **13**, 895; 1949, **14**, 79; see Hey, *Ann. Reports*, 1948, **45**, 139), and the probable mechanism of the reactions elucidated. The present paper describes homolytic addition of carbon tetrachloride to acraldehyde and its acetals, which, by analogy with Kharasch's work, would be expected to yield, as the 1 : 1 adducts, the compounds (I) and (II), respectively:

(I) $CCl_3{\cdot}CH_2{\cdot}CHCl{\cdot}CHO$ $CCl_3{\cdot}CH_2{\cdot}CHCl{\cdot}CH(OR)_2$ (II)

With acraldehyde itself, polymerisation would be expected to be a competing reaction, and in fact no simple adduct (I) could be isolated from reaction of the aldehyde with carbon

* Part III, *J.*, 1953, 1398.

tetrachloride in the presence of benzoyl peroxide or under ultra-violet irradiation. The products, white amorphous solids, always contained chlorine, but whether they were telomers or mixtures of telomers and aldehyde polymers was not ascertained. Experiments with carbon tetrabromide were no more promising, so attention was turned to acraldehyde acetals.

The peroxide-catalysed addition of acetaldehyde (Mondon, *Angew. Chem.*, 1952, **64**, 224) and butaldehyde (U.S. Rubber Co., B.P. 635,934) to acraldehyde diethyl acetal has been stated to yield the expected β-acyloxypropaldehyde diethyl acetals (III). There are, however, no reports of the addition of polyhalogenomethanes to acraldehyde acetals.

$$CH_2{:}CH{\cdot}CH(OEt)_2 + R{\cdot}CHO \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OEt)_2 \quad \text{(III)}$$

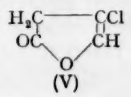
In the present work reaction of carbon tetrachloride with acraldehyde diethyl acetal under the influence of ultra-violet irradiation gave a rather complex mixture from which was isolated, in poor yield (maximum 18%, based on the acetal), a compound which was shown (see below) to be the 1 : 1-adduct, *viz.*, αγγγ-tetrachlorobutaldehyde diethyl acetal (II; R = Et). Similar results were obtained with a cyclic acetal of acraldehyde, 4-methyl-2-vinyl-1 : 3-dioxan, although the yield of 1 : 1 adduct was lower (8—9%). In both cases higher-boiling compounds derived from 1 mol. of carbon tetrachloride and 2 mols. of acetal were obtained; these compounds are considered briefly below.

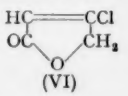
The acetals of αγγγ-tetrachlorobutaldehyde were very resistant to hydrolysis but boiling concentrated hydrochloric acid eventually furnished the free aldehyde which readily polymerised and also formed a solid hydrate; the infra-red spectrum of crystals of the latter contained a broad band with a maximum at 3250 cm.$^{-1}$ (hydroxyl group) but no bands due to a free aldehyde group. Attempted drying of the hydrate in a desiccator resulted in partial liberation of the aldehyde (weak band at 1745 cm.$^{-1}$, in CCl_4) which rapidly polymerised (set of strong bands between 970 and 1125 cm.$^{-1}$, indicative of polyaldehyde or acetal). The aldehyde (or hydrate) derived from either acetal yielded the same 2 : 4-dinitrophenylhydrazone, showing that the basic structure was the same in each case.

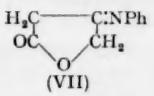
Proof of the structure of the tetrachloro-aldehyde was obtained in the following way. Oxidation of the hydrate, or of the acetals themselves, with concentrated nitric acid furnished in good yield a tetrachlorobutyric acid, which with concentrated sulphuric acid gave fumaric acid in 87% yield (based on the tetrachloro-acid). Clearly, the 1 : 1 adducts were of the type $CCl_3{\cdot}CH_2{\cdot}CHCl{\cdot}CH(OR)_2$ and not $CH_2Cl{\cdot}CH(CCl_3){\cdot}CH(OR)_2$, and the derived carboxylic acid was αγγγ-tetrachlorobutyric acid (IV). The acetal structures were

$$\underset{\text{(I)}}{CCl_3{\cdot}CH_2{\cdot}CHCl{\cdot}CHO} \xrightarrow{HNO_3} \underset{\text{(IV)}}{CCl_3{\cdot}CH_2{\cdot}CHCl{\cdot}CO_2H} \xrightarrow{H_2SO_4} CO_2H{\cdot}CH{:}CH{\cdot}CO_2H$$

confirmed by treatment with concentrated sulphuric acid at 130° for 10 min. In each case a neutral chloro-compound, m. p. 54°, $C_4H_3O_2Cl$, was obtained. This was tentatively formulated as β-chlorobut-β-enolide (V); the isomer (VI), although a possibility in view of the results of Swain, Todd, and Waring (*J.*, 1944, 548) who obtained but-α-enolides by


(V)


(VI)


(VII)

cyclisation of β-formylpropionic acids, is known (Hill and Cornelison, *Amer. Chem. J.*, 1894, **16**, 288) as a solid of m. p. 25—26°.

The monochloro-compound showed only end-absorption below 2200 Å in the ultra-violet region (ε_{2200} 8300 in EtOH) (cf. data for unsaturated lactones; Haynes and Jones, *J.*, 1946, 954; Cocker and Hornsby, *J.*, 1947, 1157; Jones and Whiting, *J.*, 1949, 1423; Young, *J. Amer. Chem. Soc.*, 1949, **71**, 1346). An infra-red band at 1794 cm.$^{-1}$ was clearly the main carbonyl band, its position indicating a but-β-enolide ring system (cf. Grove and Willis, *J.*, 1951, 877, who give 1800 and 1750 cm.$^{-1}$ for the carbonyl stretching frequency in but-β- and -α-enolides, respectively, but point out that the positions of these maxima

may be shifted considerably by substituents). A band at 1618 cm.$^{-1}$ was the main C:C band, comparable with that given by C:C in C:C·C·O– groups (cf. Nat. Bur. Stand. Catalog of Spectra, No. 143).

With 2 mols. of aniline the chloro-lactone furnished a small yield of a crystalline, chlorine-free compound which, though first formulated as β-anilinobut-β-enolide was shown (mixed m. p.; ultra-violet and infra-red absorption spectra) to be the anilino-tetronic acid described as the Δ^{α}-compound by Wolff and Schimpff (*Annalen*, **1901**, **315**, 156). The anilino-compound had an absorption maximum at 2860 Å (ε 25,100), analogous to that given by β-anilino-αα-dimethyl- (2810 Å; ε 24,000) and β-anilino-αα-pentamethylene-but-α-enolide (2810 and 2880 Å; 27,000 and 24,000, respectively) (Jones and Whiting, *loc. cit.*), but this did not definitely exclude the Δ^{β}-formulation as this compound would also be expected to absorb in this region. It did, however, eliminate a third possibility, namely, the anil (VII), whose C:NPh chromophoric system would absorb at shorter wave-lengths [Et_2C:NPh has $\lambda_{max.}$ 2500 Å, ε 12,000 (Braude, *Ann. Reports*, **1945**, **42**, 126)]. As, however, Δ^{β}-lactones are known to be isomerised to the Δ^{α}-compounds on treatment with bases (Thiele, Tischbein, and Lossow, *Annalen*, 1901, **319**, 180; Lukes, *Coll. Czech. Chem. Comm.*, 1929, **1**, 461; Pauly, Gilmour, and Will, *Annalen*, 1914, **403**, 152), it seems probable that the anilino-compound was indeed the Δ^{α}-isomer.

Hydrogenation of the chloro-lactone in an attempt to prepare the corresponding saturated lactone, β-chloro-γ-butyrolactone, resulted in extensive hydrogenolysis and some butyric acid was formed. This degradation of a βγ-unsaturated γ-lactone to the deoxy-acid was reminiscent of the results obtained by Jacobs and Scott (*J. Biol. Chem.*, 1930, **87**, 601; cf. Cocker and Hornsby, *loc. cit.*; Eisner, Elvidge, and Linstead, *J.*, 1950, 2223) for a number of unsaturated lactones; in the present case the β-chlorine atom was also hydrogenolysed. The isolation of butyric acid was further evidence for an unbranched-carbon skeleton in the original tetrachloro-aldehyde.

Dehydrochlorination of the diethyl acetal of αγγγ-tetrachlorobutaldehyde with alkali led to a trichloro-aldehyde acetal which, on the basis of spectroscopic evidence (absence of band due to *trans*-CH:CH· at about 965 cm.$^{-1}$) and its resistance to further alkaline hydrolysis, was probably the acetal of 2 : 4 : 4-trichlorobut-3-enal; the inertness of CCl_2:C groups towards attack by alkali is well known. By alternate hydrogenation and dehydrochlorination, this acetal was converted into a mixture containing butaldehyde diethyl acetal; this provided further evidence for the straight-chain nature of the original tetrachlorobutaldehyde, although the yield of butaldehyde 2 : 4-dinitrophenylhydrazone finally isolated was not very high.

The high-boiling products obtained in the addition of carbon tetrachloride to acraldehyde diethyl acetal were examined only briefly. They contained the adduct derived from 1 mol. of the tetrahalide and 2 mols. of the acetal but this material could not be isolated in a pure state. It readily lost ethanol, forming a thermolabile unsaturated compound whose absorption spectrum contained bands at 711 and 1675 cm.$^{-1}$; these, by analogy with the bands at 733 and 1660 cm.$^{-1}$ given by *cis*-but-1-enyl butyl ether (Hall, Philpotts, Stern and Thain, *J.*, 1951, 3341), indicated the presence of a substituted *cis*-αβ-unsaturated ether grouping. The 1 : 2 adduct derived from the cyclic acetal of acraldehyde was more stable than that from the diethyl acetal and was obtained reasonably pure.

An attempt to use initiation by benzoyl peroxide for the reaction between carbon tetrachloride and acraldehyde diethyl acetal was unsuccessful, the only identifiable product being 1 : 1 : 3-triethoxypropane.

Experimental

Reaction of Carbon Tetrachloride with Acraldehyde.—(*a*) Refluxing a mixture of acraldehyde (65 g.), carbon tetrachloride (1200 g.), and benzoyl peroxide (5 g.) for 19 hr. afforded only an amorphous solid (27 g.) containing 10% of chlorine.

(*b*) Addition of acraldehyde (56 g.) in carbon tetrachloride (250 ml.) during 18 hr. to benzoyl peroxide (5 g.) in refluxing carbon tetrachloride (500 ml.), followed by a further 8 hours' boiling, filtration, and further refluxing of the filtrate after addition of more peroxide, yielded polymer (39 g.) containing 23% of chlorine.

(*c*) Refluxing acraldehyde (56 g.) in carbon tetrachloride (750 ml.) for 24 hr. under ultra-violet irradiation gave only a solid polymer (2 g.) containing 8% of chlorine.

Reaction of Carbon Tetrabromide with Acraldehyde.—Refluxing carbon tetrabromide (166 g.), carbon tetrachloride (600 ml.), and acraldehyde (28 g.) for 48 hr., with addition of benzoyl peroxide (2·5-g. portions) after 0, 7, and 24 hr., or refluxing a mixture of carbon tetrabromide (200 g.), acraldehyde (10·1 g.), and carbon tetrachloride (200 g.) for 5 hr. under ultra-violet irradiation afforded in each case only dark residues.

Reaction of Carbon Tetrachloride with Acraldehyde Diethyl Acetal.—In a typical experiment, the acetal (65 g., 0·5 mole) and carbon tetrachloride (1200 g.) were refluxed in a Pyrex flask under ultra-violet irradiation for 22 hr., then washed with dilute sodium hydrogen carbonate solution; the excess of carbon tetrachloride was distilled off at atmospheric pressure, followed by unchanged acetal (approx. 17 g.) at 70 mm., and the residue then fractionated at 0·5—1·0 mm., the lower-boiling product being taken off through a helices-packed column (35 × 1 cm.) and the higher-boiling material through a short Vigreux column. The main fractions were: (i) b. p. 100—106°/1 mm. (25·7 g.), n_D^{20} 1·4654—1·4668, and (ii) b. p. 142—143°/0·5—1·0 mm. (12·8 g.), n_D^{20} 1·471—1·473.

A middle cut of fraction (i) had b. p. 105°/1 mm., n_D^{20} 1·4668 (Found: C, 33·95; H, 5·55; Cl, 49·9. $C_8H_{14}O_2Cl_4$ requires C, 33·85; H, 4·95; Cl, 49·95%); this was *αγγγ-tetrachlorobutaldehyde diethyl acetal.* Fraction (ii) could not be purified; on redistillation it gradually decomposed with the production of an αβ-unsaturated ether; *e.g.*, a fraction of b. p. 131°/0·4 mm., n_D^{20} 1·4717, thus obtained was found (by infra-red examination) to contain about 10% of the unsaturated ether. Repeated fractionation increased this amount.

In an experiment in which the washing with sodium hydrogen carbonate was omitted, a slow decomposition of the contents of the distilling-flask took place after the tetrachlorobutaldehyde had been collected, the volatile products of the decomposition being condensed in a trap at −80°, and in place of fraction (ii) above there was obtained a liquid, b. p. 145—150°/0·5—1·0 mm., n_D^{20} 1·4917—1·4930, which was largely the αβ-unsaturated ether derived from the adduct of 1 mol. of carbon tetrachloride and 2 mols. of acraldehyde diethyl acetal by elimination of 1 mol. of ethanol (Found: C, 42·05; H, 5·75; Cl, 40·2. Calc. for $C_{13}H_{22}O_3Cl_4$: C, 42·4; H, 6·05; Cl, 38·55%). Attempts to purify this by refractionation were unsuccessful.

The trap contents obtained above contained ethanol and hydrogen chloride, and afforded a 2 : 4-dinitrophenylhydrazone which, recrystallised from ethanol, formed needles, m. p. 122° alone or mixed with authentic β-*chloropropaldehyde* 2 : 4-*dinitrophenylhydrazone*, m. p. 122° (Found: C, 40·2; H, 3·5; N, 20·6; Cl, 12·8. $C_9H_9O_4N_4Cl$ requires C, 39·6; H, 3·35; N, 20·6; Cl, 13·0%), obtained from β-chloropropaldehyde diethyl acetal prepared by Crawford and Kenyon's method (*J.*, 1927, 396).

αγγγ-Tetrachlorobutaldehyde.—The above diethyl acetal (10 g.) was added to aqueous hydrochloric acid (50 ml.; 15% w/v), and the mixture refluxed for 18 hr. Steam-distillation afforded a pale yellow oil which solidified almost completely in contact with water. The solid was triturated with light petroleum (b. p. 40—60°), filtered off, and washed with more of the solvent. A crystalline white solid (4 g.), m. p. 50—51°, was obtained, which liquefied in a vacuum-desiccator. The crystalline *hydrate* was dried for analysis in the following manner; a sample was kept at room temperature at 0·2 mm. for about 2 hr., washed with light petroleum (b. p. 40—60°) to remove traces of free aldehyde, and re-dried at room temperature at 0·2 mm. for 10 min. (Found: C, 21·5; H, 2·8; Cl, 62·0. $C_4H_4OCl_4,H_2O$ requires C, 21·1; H, 2·65; Cl, 62·25%). In a later experiment the free aldehyde was isolated (by ether-extraction of the steam-distillate) and found to have b. p. 83—85°/12 mm., n_D^{20} 1·4982; it polymerised before it could be analysed.

Addition of a methanolic solution of the free aldehyde, or its hydrate, to a saturated solution of 2 : 4-dinitrophenylhydrazine in aqueous 2N-hydrochloric acid gave the 2 : 4-*dinitrophenylhydrazone*, which separated from methanol as yellow needles, m. p. 124—125° (Found: C, 30·6; H, 2·2; N, 14·4; Cl, 36·2. $C_{10}H_8O_4N_4Cl_4$ requires C, 30·8; H, 2·05; N, 14·35; Cl, 36·3%). Attempts to prepare this derivative by treating the diethyl acetal directly with ethanolic sulphuric acid or aqueous hydrochloric acid solutions of 2 : 4-dinitrophenylhydrazine gave only unstable uncrystallisable gums. Although the crystalline derivative was stable in the solid state it decomposed slowly in methanol at room temperature.

αγγγ-Tetrachlorobutyric Acid.—αγγγ-Tetrachlorobutaldehyde diethyl acetal (10 g.) was added dropwise to nitric acid (70 ml.; 70% w/v) at 50—60° during 3 hr. The mixture was then heated at 100° for 30 min., poured into cold water (500 ml.), and extracted with ether. A strong smell of chloropicrin was noticed. The ether extract was shaken with sodium hydrogen

carbonate solution, and the aqueous alkaline solution separated, acidified, and extracted with ether. The ether extract was dried (Na_2SO_4), the solvent distilled off, and the residual liquid fractionated through a small Vigreux column. A colourless oil (5·8 g., 73%), b. p. 117—120°/0·5 mm., n_D^{20} 1·4992, was obtained, which solidified at −40°. Recrystallisation from light petroleum (b. p. 40—60°) at −50° afforded *αγγγ-tetrachlorobutyric acid*, m. p. 27—29° (Found: C, 21·4; H, 1·8; Cl, 62·3. $C_4H_4O_2Cl_4$ requires C, 21·25; H, 1·8; Cl, 62·75%). Its p-*phenylphenacyl* ester had m. p. 96° after recrystallisation from ethanol (Found: C, 51·3; H, 3·55. $C_{18}H_{14}O_3Cl_4$ requires C, 51·45; H, 3·35%). The *anilide*, prepared by way of the acid chloride (thionyl chloride under reflux), separated from aqueous ethanol (50%) in colourless needles, m. p. 124° (Found: C, 39·85; H, 3·05; N, 4·95; Cl, 46·9. $C_{10}H_9ONCl_4$ requires C, 39·9; H, 3·0; N, 4·65; Cl, 47·1%).

Reaction of αγγγ-Tetrachlorobutyric Acid with Concentrated Sulphuric Acid.—(*a*) A solution of the butyric acid (2 g.) in concentrated sulphuric acid (10 g.) was heated at 130° for 10 min., cooled, and poured on crushed ice. The mixture obtained was extracted continuously with ether, the dried (Na_2SO_4) ether extract evaporated on the steam-bath, and the residue (0·5 g.) recrystallised from water. The product did not melt in an open tube but gradually sublimed above 200°. A sample purified by sublimation was shown by infra-red spectroscopic examination to be mainly (more than 90%) fumaric acid. The di-*p*-nitrobenzyl ester prepared from it had m. p. 147—149°, and the mixed m. p. with authentic fumaric ester (m. p. 150—152°) was 149—151°.

(*b*) A solution of *αγγγ*-tetrachlorobutyric acid (4·37 g.) in concentrated sulphuric acid (25 ml.) was heated at 130° until evolution of hydrogen chloride ceased (approx. 1 hr.), cooled, and poured on crushed ice (100 g.). The mixture obtained was extracted continuously with ether, and the extract evaporated on the steam-bath. The residue was dissolved in water (50 ml.), thiourea (0·2 g.) added, and the solution refluxed for 24 hr. to isomerise any maleic acid to fumaric acid. The cooled product was filtered, and the precipitate washed with cold water (5 ml.) and dried to constant weight in a vacuum-desiccator. The fumaric acid thus obtained weighed 1·95 g. (87%) and had m. p. 292° in a sealed tube (recorded m. p.s range from 287° to 295°).

Reaction of αγγγ-Tetrachlorobutaldehyde Diethyl Acetal with Concentrated Sulphuric Acid.—A solution of the acetal (10 g.) in concentrated sulphuric acid (50 ml.) was heated at 130° for 10 min. Considerable charring occurred. The product was poured on crushed ice (100 g.) and extracted continuously with ether. The ethereal solution was dried and evaporated to dryness, and the residue recrystallised from light petroleum (b. p. 60—80°). White, needle-like crystals (1·1 g.) of *β-chlorobut-β-enolide* were obtained, which, after two further recrystallisations from the same solvent, had m. p. 54° (Found: C, 40·95; H, 2·8; Cl, 29·3. $C_4H_3O_2Cl$ requires C, 40·55; H, 2·55; Cl, 29·95%). Ultra-violet absorption in ethanol: increasing absorption down to 2200 Å (ε 8300); no maxima.

A solution of the lactone (1 mol.) in aniline (2 mols.) solidified overnight. The solid was dissolved in ethanol, the solution poured into a large volume of dilute hydrochloric acid, and the precipitate filtered off and washed with water, then with dilute ammonia, and finally with water. Recrystallisation from ethanol gave creamy-white nodules, m. p. 222° (Found: C, 68·3; H, 5·5; N, 8·15; Cl, absent. Calc. for $C_{10}H_9O_2N$: C, 68·55; H, 5·2; N, 8·0%). Ultra-violet absorption in ethanol: max. 2860 Å (ε 25,100). The m. p. was undepressed on admixture of the crystals with authentic anilinotetronic acid (β-anilinobut-α-enolide) of m. p. 220—221°, prepared by the method of Wolff and Schimpff (*loc. cit.*), which had identical ultra-violet and infra-red absorption spectra.

Hydrogenation of β-Chlorobut-β-enolide.—Hydrogenation of the chloro-lactone (0·4 g.) in dry ether (25 ml.) over Adams's catalyst (0·05 g.) resulted in absorption of 161 ml. (N.T.P.) of hydrogen and formation of 1·05 equiv. of acid (titre = 3·60 ml. of N-NaOH). The sodium salt of the acid produced was isolated and converted by way of the acid chloride into the anilide which, crystallised from water, had m. p. 96°, undepressed on admixture with authentic *n*-butyranilide, m. p. 97°.

Dehydrochlorination of αγγγ-Tetrachlorobutaldehyde Diethyl Acetal.—A mixture of the acetal (10 g.) and a solution of potassium hydroxide (2·5 g., 1·25 equivs.) in absolute ethanol (70 ml.) was refluxed for 4 hr. The potassium chloride which separated was filtered off, the filtrate concentrated on the steam-bath to remove ethanol, and the residue diluted with ether. The ether solution was washed with water and dried, the solvent distilled off, and the residual liquid fractionated, giving a colourless liquid (7·2 g.), b. p. 110—112°/13 mm., n_D^{20} 1·4683, which on the basis of infra-red spectroscopic analysis was probably 2 : 4 : 4-trichlorobut-3-enal diethyl

acetal (Found : C, 39·3; H, 5·45; Cl, 42·3. Calc. for $C_8H_{13}O_2Cl_3$: C, 38·8; H, 5·3; Cl, 42·9%). Attempts to prepare a 2 : 4-dinitrophenylhydrazone from it were unsuccessful.

The trichloro-compound was hydrogenated in ethanol solution over Adams's catalyst until absorption of gas ceased, treated with ethanolic potassium hydroxide solution, and re-hydrogenated alternately until three dehydrochlorinations and three hydrogenations had been performed. No purification was attempted at any stage except to remove solid material. The final ethanolic solution obtained was poured into a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Fractional crystallisation of the product afforded butaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 118—119°; mixed m. p. with authentic material (m. p. 120—120·5°) 119—120°.

Reaction of Carbon Tetrachloride with Acraldehyde Diethyl Acetal in the Presence of Benzoyl Peroxide.—A solution of the acetal (65 g.) in carbon tetrachloride (800 g.) was refluxed for 36 hr. with the addition of benzoyl peroxide (2·5 g. each time) at 0, 12, and 24 hr. Isolation of the product afforded a main fraction (30 g.), b. p. 39—40°/0·5 mm., which was largely 1 : 1 : 3-triethoxypropane (infra-red analysis; mixed m. p. of derived 2 : 4-dinitrophenylhydrazone with authentic β-ethoxypropaldehyde 2 : 4-dinitrophenylhydrazone); no other compounds were identified.

Addition of Carbon Tetrachloride to 4-Methyl-2-vinyl-1 : 3-dioxan.—A solution of the cyclic acetal (64 g.) in carbon tetrachloride (1200 g.) was refluxed for 24 hr. under ultra-violet irradiation. The excess of carbon tetrachloride was then removed on the water-bath, and the residual liquid distilled without fractionation at 1 mm. pressure. The distillate consisted of : (i) 20 g. (approx.), b. p. below 190°; (ii) 40—45 g., b. p. 190—200°; and (iii) residue (10 g.). Fraction (ii) on cooling became glassy, but could not be induced to crystallise. It was probably 1 : 5 : 5 : 5-*tetrachloro*-1 : 3-*di*-(4-*methyl*-1 : 3-*dioxan*-2-*yl*)*pentane* (Found : Cl, 34·3. $C_{15}H_{24}O_4Cl_4$ requires Cl, 34·55%).

A further experiment in which the reaction mixture was irradiated but not heated gave similar results. The crude reaction mixture in both cases was much less coloured than that obtained when using acraldehyde diethyl acetal, and the absence of decomposition during distillation was also in marked contrast to that which occurred on working up reaction mixtures from the latter acetal.

The low-boiling fractions from each experiment with the cyclic acetal were bulked and refractionated at about 0·5 mm. : no sharp separation into fractions was found over the range 33—115°/0·5 mm., but then a largely homogeneous fraction (24·2 g.), b. p. 115—120°/0·5 mm., was obtained, which on further fractionation afforded 4-*methyl*-2-1′ : 3′ : 3′ : 3′-*tetrachloropropyl*-1 : 3-*dioxan* (*i.e.*, the 1 : 1 adduct), b. p. 108—112°/0·3 mm., n_D^{20} 1·4926 (Found : C, 34·95; H, 4·2; Cl, 50·8. $C_8H_{12}O_2Cl_4$ requires C, 34·1; H, 4·3; Cl, 50·3%). Satisfactory analytical figures for carbon could not be obtained.

A portion of the pure material was refluxed for 8 hr. with concentrated hydrochloric acid, then steam-distilled, and the distillate was extracted with ether. Evaporation of the dried ether solution and distillation of the residual liquid *in vacuo* furnished approximately equal quantities of an aldehyde, b. p. 83—85°/12 mm., n_D^{20} 1·4982, and unchanged acetal, b. p. 145—150°/12 mm., n_D^{20} 1·4937. The 2 : 4-dinitrophenylhydrazone prepared from the former had m. p. 126° [mixed m. p. with αγγγ-tetrachlorobutaldehyde 2 : 4-dinitrophenylhydrazone (m. p. 124°, above) 123—125°].

Another portion of the 4-methyl-2-1′ : 3′ : 3′ : 3′-tetrachloropropyl-1 : 3-dioxan, on treatment with concentrated sulphuric acid at 130° as described on p. 2038 for tetrachlorobutaldehyde diethyl acetal, furnished the same chloro-lactone, β-chlorobut-β-enolide (m. p. and mixed m. p. 54°).

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Addition of Free Radicals to Unsaturated Systems. Part IX. The Direction of Free-radical Addition to Allene and Allyl Chloride.*

By R. N. Haszeldine, K. Leedham, and B. R. Steele.

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The photochemical reaction of trifluoroiodomethane with allene yields only the compound $CF_3{\cdot}CH_2{\cdot}CI{:}CH_2$, and radical attack is thus exclusively on the CH_2 group of allene. The synthesis of 4 : 4 : 4-trifluorobut-1-ene, 4 : 4 : 4-trifluorobuta-1 : 2-diene [(trifluoromethyl)allene], and 4 : 4 : 4-trifluorobut-1-yne is described. Trifluoroiodomethane reacts with allyl chloride to give only $CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CH_2Cl$, thus establishing the direction of radical attack on this olefin. The results are discussed briefly.

When reagents react with allene, by a mechanism involving addition of ionic intermediates, it is known that the polarisation of the allene is represented as $\overset{\delta-}{C}H_2{=}\overset{\delta+}{C}{=}CH_2$ (*e.g.*, EtOH, H_2O, HOCl,HF; see Whitmore, "Organic Chemistry," Chapman and Hall, Ltd., London, 1937, p. 50; HF, Austin, U.S.P. 2,585,529/1952). The photochemical reaction of trifluoroiodomethane with allene has now been investigated in order to determine the direction of free-radical attack.

Trifluoroiodomethane and allene do not react in the dark, but a smooth reaction occurs on exposure to ultra-violet light, to give a high yield of a compound $CF_3{\cdot}(C_3H_4){\cdot}I$ (b. p. 102°). This could be (I) or (II), formed by a chain reaction of the type described in earlier Parts, *e.g.*:

(I) $CF_3{\cdot}CH_2{\cdot}CI{:}CH_2$ $\qquad$ $CF_3{\cdot}C(:CH_2){\cdot}CH_2I$ (II)

$$CF_3{\cdot} + CH_2{:}C{:}CH_2 \longrightarrow CF_3{\cdot}CH_2{\cdot}\dot{C}{:}CH_2$$

$$CF_3{\cdot}CH_2{\cdot}\dot{C}{:}CH_2 + CF_3I \longrightarrow CF_3{\cdot}CH_2{\cdot}CI{:}CH_2 + CF_3{\cdot} \longrightarrow \text{etc.}$$

The ultra-violet spectrum of the product is very similar to that of the known isomer 4 : 4 : 4-trifluoro-2-iodobut-2-ene (b. p. 94·5°), as shown in the annexed Table, and this strongly suggests that the product is (I), which also contains the $\cdot CH_2{\cdot}CI{:}CH_2$ system (with a vinylic iodine atom). The ultra-violet spectrum of (II) would be very similar to that of allyl iodide which has a single maximum at much longer wave-length and no high-intensity absorption at shorter wave-lengths (see Table).

Ultra-violet spectra (in light petroleum).

	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$		$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$
$CF_3{\cdot}CH_2{\cdot}CI{:}CH_2$	261	315	242	150	$CF_3{\cdot}CH{:}CI{\cdot}CH_3$[1]	260	350	251·5	320
	223	3500	—	—		230	3800	221·5	3100
$CH_2I{\cdot}CH{:}CH_2$[2]	271	800	249·5	490		215	3500	—	—

[1] Leedham and Haszeldine (*J.*, 1954, 1634). [2] Haszeldine (*J.*, 1953, 1764).

Distinction between (I) and (II) can also be made on the basis of infra-red spectra. The product shows a strong C:C stretching absorption at 6·17 μ which is in the characteristic region for compounds containing a vinylic iodine atom. The C:C absorption in (II) would be close to that in 3 : 3 : 3-trifluoro-2-methylpropene, *i.e.*, near 6·0 μ. The $>C{:}CH_2$ group is also shown by the very strong band at 10·93 μ, which is displaced from its characteristic position in hydrocarbon olefins (11·24 μ).

Chemical evidence in favour of (I) is its reaction with zinc and mineral acid to give 4 : 4 : 4-trifluorobut-1-ene (III); (II) would have given 3 : 3 : 3-trifluoro-2-methylpropene (IV) by this reaction. The $\cdot CH{:}CH_2$ group is revealed by the bands in the infra-red at 3·22 (vinylic C–H), 6·06 (C:C stretching) (cf. $CH_3{\cdot}CH{:}CH_2$, C:C 6·06 μ), and 10·10, 10·75 μ (cf. compounds of type $R{\cdot}CH{:}CH_2$, 10·1, 10·9 μ). The b. p.s and double-bond stretching vibrations of the known isomeric trifluorobutenes are $CF_3{\cdot}CH{:}CH{\cdot}CH_3$ 17°, 5·90 μ; $CF_3{\cdot}CMe{:}CH_2$ 6·4°, 6·0 μ.

Since (III) was obtained in high yield, and with no contamination by (IV), the product

* Part VIII, *J.*, 1954, 1634.

from trifluoroiodomethane and allene is exclusively (I), *i.e.*, attack of the trifluoromethyl radical is on the CH_2 group of allene. Final proof of constitution is given by the synthesis of (III) by an independent unambiguous route. Trifluoroiodomethane and allyl chloride,

$CF_3 \cdot CH_2 \cdot CH{:}CH_2$ (III) $\quad CF_3 \cdot CMe{:}CH_2$ (IV) $\quad CF_3 \cdot CH_2 \cdot CHI \cdot CH_2Cl$ (V) $\quad (CF_3)(CH_2Cl)CH \cdot CH_2I$ (VI)

on exposure to ultra-violet light, readily give 1-chloro-4 : 4 : 4 -trifluoro-2-iodobutane (V). Dehalogenation by means of zinc and ethanol gives a high yield of a trifluorobutene which is spectroscopically identical with (III). It is to be noted that if the attack of the trifluoromethyl radical had been on the $\cdot CH{:}$ group of allyl chloride to give (VI), dehalogenation could have yielded neither (III) nor (IV). The direction of addition of the trifluoromethyl radical to allene and to allyl chloride is thus conclusively proved. Only very small amounts of fluoroform were detected in the reaction products from allene and allyl chloride, *i.e.*, hydrogen-abstraction is not a major reaction. The propagation step is not favoured (see earlier papers), since only small amounts of product with a higher b. p. were formed during reaction.

4 : 4 : 4-Trifluoro-2-iodobut-1-ene with ethanolic potassium hydroxide gives a mixture of 4 : 4 : 4-trifluorobuta-1 : 2-diene (VII) and 4 : 4 : 4-trifluorobut-1-yne (VIII). The

$CF_3 \cdot CH{:}C{:}CH_2$ (VII) $\quad CF_3 \cdot CH_2 \cdot C{:}CH$ (VIII) $\quad CF_3 \cdot C{:}C \cdot CH_3$ (IX)

latter is easily detected by its acetylenic carbon–hydrogen vibration at 3·00 μ and the C:C stretching absorption at 4·33 μ; it is separated from the trifluoromethylallene (VII) by formation of a silver salt, from which it can be regenerated on treatment with acid. The allene (VII) shows the $\cdot CH{:}C{:}CH_2$ bands in the infra-red at 5·00, 5·08 (doubtlet), and 5·90 μ (cf. methylallene 5·10, 5·88 μ); there are no bands corresponding to the C:C stretching vibration or to an acetylenic carbon–hydrogen absorption. The isomeric 1 : 1 : 1-trifluorobut-2-yne (IX) was described in Part VIII. The b.p.s of the isomers are similar: (VII), 16°; (VIII), 15°; (IX), 18·0—18·5°. The alkyne (VIII) is doubtless formed by isomerisation of the allene (VII) in the alkaline medium, just as allene is isomerised to propyne when treated with sodium.

By adopting the concept that intermediate radical stability determines the direction of radical addition to an unsaturated compound (see earlier papers), it follows that relative radical stabilities are: $CF_3 \cdot CH_2 \cdot \dot{C}{:}CH_2 > CH_2{:}\dot{C}(CF_3) \cdot CH_2 \cdot$; $CF_3 \cdot CH_2 \cdot \dot{C}H \cdot CH_2Cl > (CF_3)(CH_2Cl)CH \cdot \dot{C}H_2 \cdot$. Full discussion is deferred until a later paper.

Experimental

Allene was prepared from allyl bromide and was shown to be free from impurities (particularly methylacetylene) by infra-red spectroscopic examination. Allyl chloride was a commercial sample distilled in nitrogen immediately before use; it was peroxide-free. Oxygen, moisture, etc., which might catalyse ionic or free-radical reactions were excluded. Silica or Pyrex vessels were thoroughly cleaned, and were filled and sealed *in vacuo*. A Hanovia S-250 ultra-violet lamp was used.

Reaction of Trifluoroiodomethane with Allene.—Trifluoroiodomethane (37·9 g., 0·193 mole) and allene (7·80 g., 0·195 mole), sealed in a silica tube, were exposed to ultra-violet light for 48 hr. to give products (15·25 g.) of b. p. >0°. When distilled, they gave 4 : 4 : 4-*trifluoro*-2-*iodobut*-1-*ene* (14·61 g., 96%), b. p. 101—102·5°, 58—59°/160 mm., n_D^{20} 1·4312 (Found: C, 20·8; H, 2·0. $C_4H_4IF_3$ requires C, 20·4; H, 1·7%), and a small amount of material of higher b. p. which was not examined.

4 : 4 : 4 -Trifluoro-2-iodobut-1-ene (5·28 g.) was added to zinc powder (25 g.), magnesium (2 g.), and 50% hydrochloric acid (10 ml.) in a flask fitted with reflux water-condenser leading *via* rubber tubing to a trap cooled in liquid oxygen. The temperature was raised to 100° during 3 hr. and the volatile product was distilled *in vacuo*, to give 4 : 4 : 4-trifluorobut-1-ene (82%), b. p. (isoteniscope) 10·6°, shown to be identical with the material prepared below by comparison of infra-red spectra.

In control experiments, allene was irradiated alone, or in presence of iodine, for 3 days; infra-red spectroscopic examination showed that allene did not isomerise to propyne under these conditions.

Reaction of Trifluoroiodomethane with Allyl Chloride.—Freshly distilled allyl chloride (5·6 g., 0·073 mole; b. p. 45·5°/769 mm.) and trifluoroiodomethane (15·3 g., 0·078 mole) in a Pyrex tube were exposed to ultra-violet light (14 days). The volatile products were distilled, to give trifluoroiodomethane (8·6 g., 56%). Distillation of the liquid products in an atmosphere of nitrogen gave allyl chloride (3·5 g., 60%) and 1-*chloro*-4 : 4 : 4-*trifluoro*-2-*iodobutane* (8·3 g., 89%), b. p. 88°/69 mm., n_D^{20} 1·476 (Found: C, 18·0; H, 1·7. $C_4H_5ClIF_3$ requires C, 17·6; H, 1·8%).

4 : 4 : 4-*Trifluorobut*-1-*ene*.—1-Chloro-4 : 4 : 4-trifluoro-2-iodobutane (2·80 g.) and ethanol (3 ml.), added slowly to zinc dust (10 g.) and refluxing ethanol (20 ml.), gave volatile products, which were washed with water and distilled to give 4 : 4 : 4-*trifluorobut*-1-*ene* (0·92 g., 80%), b. p. 10·5° (Found: C, 43·5; H, 5·6%; *M*, 111. $C_4H_5F_3$ requires C, 43·6; H, 4·5%; *M*, 110).

4 : 4 : 4-*Trifluorobuta*-1 : 2-*diene*.—To 4 : 4 : 4-trifluoro-2-iodobut-1-ene (2·90 g.) was slowly added, with stirring, ethanolic potassium hydroxide (10 ml. of 10%). After 2 hr. at room temperature the mixture was refluxed for 2 hr. The combined volatile products, which had passed through a reflux water-condenser and been condensed in a trap cooled by liquid oxygen, were distilled *in vacuo*, to give a mixture (0·98 g.) of an allene and an acetylene. This product was repeatedly shaken with a solution of silver nitrate (2 *g.*) in 50% aqueous ethanol (10 ml.) until the volatile material was shown by its infra-red spectrum to be free from acetylenic compounds. Redistillation gave 4 : 4 : 4-*trifluorobuta*-1 : 2-*diene* (0·581 g., 44%), b. p. 16·0° (Found: C, 44·2%; *M*, 108·5. $C_4H_3F_3$ requires C, 44·5%; *M*, 108).

The white precipitate obtained from the above reaction with silver nitrate was treated with sulphuric acid (3 ml. of 30%), and the gaseous product was distilled *in vacuo*, to give 4 : 4 : 4-*trifluorobut*-1-*yne* (0·290 g., 22%), b. p. 15° (Found: F, 52·4%; *M*, 108. $C_4H_3F_3$ requires F, 52·7%; *M*, 108).

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Eight- and Higher-membered Ring Compounds. Part XI. Alkyl Derivatives of Di-, Tri-, and Tetra-salicylides.*

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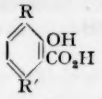
The use of tri-*o*-thymotide as a reagent for the resolution of racemates with which it forms crystalline inclusion compounds has prompted the investigation of related substances. Intermolecular dehydration of 3-*tert.*-butyl-6-methyl-, 3 : 6-dimethyl-, 3-phenyl-, 3-methyl-6-*iso*propyl-, and 6-methyl-4-*iso*propyl-salicylic acids has given products of the type of di-, tri-, and tetra-salicylide, but none of them gave crystalline inclusion compounds.

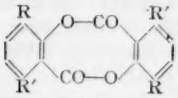
TRI-*o*-THYMOTIDE (III; R = Pr^i, R′ = Me), prepared by intermolecular dehydration of *o*-thymotic acid (I; R = Pr^i, R′ = Me) (Part VI, Baker, Gilbert, and Ollis, *J.*, 1952, 1443), is of unusual interest. Steric interaction between the carbonyl-oxygen atoms and the *iso*propyl groups prevents the molecule from assuming a planar configuration, and it takes up enantiomorphous, pyramidal forms, possessing three-fold axes of symmetry. Tri-*o*-thymotide forms many crystalline inclusion compounds, some of which, *e.g.*, the complexes with *n*-hexane and benzene, are spontaneously resolved (Powell and Newman, *J.*, 1952, 3747). More importantly, crystallisation of tri-*o*-thymotide with a racemic adduct may effect simultaneous resolution of both substances, thus providing a method of resolution (of, *e.g.*, 2-bromobutane) which is independent of the chemical nature of the substance to be resolved and, unlike the classical method of resolution, requires no previously optically active material (Powell, *Nature*, 1952, **170**, 155) [cf. the resolutions of 2-chloro-octane by repeated crystallisation of its adduct with urea (Schlenk, *Analyst*, 1952, **77**, 870)].

It is possible that other substances, related to tri-*o*-thymotide, may form inclusion

* Part X, *J.*, 1952, 3163.

compounds with a different range of adducts, some of which may undergo spontaneous resolution. With the object of adding to the scope of the new method, we have, therefore, prepared anhydro-derivatives of several acids related to *o*-thymotic acid, in particular 3-*tert.*-butyl-6-methylsalicylic acid (I; R = Me, R′ = Bu^t). In a trianhydro-compound


(I)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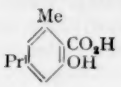
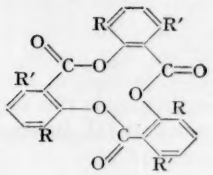
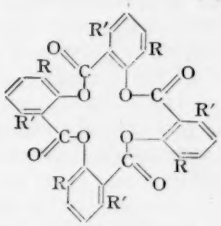

(V)

(III)




(IV)

of this acid (III; R = Me, R′ = Bu^t), the steric interference between the carbonyl-oxygen atoms and the *tert.*-butyl groups would cause a greater departure from planarity, and therefore a greater difference between the enantiomorphous forms, than in the case of tri-*o*-thymotide. There was the possibility, therefore, that it might exist in more stable enantiomorphous forms than tri-*o*-thymotide, and might be a better resolving agent.

2-*tert.*-Butyl-5-methylphenol was most conveniently prepared (50% yield) from *m*-cresol by reaction with *tert.*-butyl alcohol and anhydrous ferric chloride at room temperature (Nazarova and Tsukervanik, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 1151); with zinc chloride as condensing agent at 100° (Stockelbach, U.S.P. 1,982,180) we obtained a 45% yield, and the product was difficult to purify. The descriptions of 2-*tert.*-butyl-5-methylphenol do not entirely agree. Tchitchibabine (*Bull. Soc. chim.*, 1935, **2**, 502) describes it as a hygroscopic solid, m. p. 23°, giving a monohydrate, m. p. 37°; Stockelbach records a labile form, m. p. 34—35°, and a stable form, m. p. 23·1°; "Koppers Technical Bulletin" C-2-130 (1952, Koppers Co., Inc., U.S.A.) gives m. p. 22·7°, and a hydrate with $\frac{1}{4}H_2O$, m. p. 37°. We find that the anhydrous compound has m. p. 23°, and that it slowly absorbs moisture from air and first liquefies and then solidifies, giving finally a hydrate, m. p. 37°, analysis of which agrees best with $\frac{1}{3}$ molecule of water.

Carboxylation of 2-*tert.*-butyl-5-methylphenol by the Kolbe reaction according to Lespagnol and Bar (*Bull. Soc. chim.*, 1938, **5**, 1360) gave a 30% yield of 3-*tert.*-butyl-6-methylsalicylic acid (I; R = Bu^t, R′ = Me), but the modification now described gives an 85% yield. Distillation of the *O*-acetyl derivative of this acid gave acetic acid, and, as the only other isolable product, di-(3-*tert.*-butyl-6-methylsalicylide) (II; R = Bu^t, R′ = Me). This dianhydro-compound was also obtained as the only product of the dehydration of the free acid with phosphorus oxychloride or phosphoric anhydride in xylene. Under all these three conditions, *o*-thymotic acid gives a mixture of di- and tri-*o*-thymotide.

3 : 6-Dimethylsalicylic acid (I; R = R′ = Me), m. p. 195°, had been previously prepared by oxidation of 4 : 7-dimethylcoumaranone (Stollé and Knebel, *Ber.*, 1921, **54**, 1220), but it has now been prepared directly from 2 : 5-dimethylphenol by the Kolbe reaction. The nature of the product, m. p. 137°, obtained by Oliveri (*Gazzetta*, 1882, **12**, 166) by heating 2 : 5-dimethylphenol and sodium in carbon dioxide, and claimed to be 3 : 6-dimethylsalicylic acid, remains obscure. When dehydrated with phosphorus oxychloride 3 : 6-dimethylsalicylic acid gave di- and tri-(3 : 6-dimethylsalicylide) (II and III; R = R′ = Me). Di-(3 : 6-dimethylsalicylide) was obtained by distillation of the *O*-acetyl derivative of the acid.

3-Phenylsalicylic acid (I; R = Ph, R′ = H) when treated with phosphorus oxychloride gave only tetra-(3-phenylsalicylide) (IV; R = Ph, R′ = H).

3-Methyl-6-*iso*propylsalicylic acid [*o*-carvacrotic acid (I; R = Me, R′ = Pr^i)] was prepared from carvacrol by Kolbe's method in 80% yield. Distillation of the *O*-acetyl derivative of the acid gave di-(3-methyl-6-*iso*propylsalicylide) (II; R = Me, R′ = Pr^i), and treatment of the free acid with phosphorus oxychloride gave a mixture of di- and tri-(3-methyl-6-*iso*propylsalicylide) (II and III; R = Me, R′ = Pr^i). Dehydration of the acid with phosphoric anhydride in xylene again gave the di- and tri-anhydro-derivatives, and 1% of tetra-(3-methyl-6-*iso*propylsalicylide) (IV; R = Me, R′ = Pr^i).

3-Methyl-5-*iso*propylphenol gave an acid by the Kolbe reaction which is assumed to be 6-methyl-4-*iso*propylsalicylic acid (V) because the alternative structure, 4-methyl-6-*iso*propylsalicylic acid, is less likely for steric reasons. Distillation of the *O*-acetyl derivative of (V) gave di-(6-methyl-4-*iso*propylsalicylide), and dehydration of the acid (V) with either phosphorus oxychloride or phosphoric anhydride gave tri-(6-methyl-4-*iso*propylsalicylide).

Hydrolysis of all the foregoing anhydro-derivatives regenerated the original acids. None of them formed inclusion compounds with ethanol, chloroform, benzene, or *m*-xylene, solvents which all give crystal complexes with tri-*o*-thymotide (for other inclusion complexes formed by compounds of the salicylide type, see Part III, Baker, Gilbert, Ollis, and Zealley, *J.*, 1951, 211).

Experimental

Molecular weights were determined ebullioscopically in benzene (unless otherwise stated) in the Menzies–Wright apparatus as described by Baker, Ollis, and Zealley (Part II, *J.*, 1951, 208).

2-Hydroxy-3 : 6-dimethylbenzoic Acid (3 : 6-*Dimethylsalicylic Acid*) (I; R = R′ = Me).—2 : 5-Dimethylphenol (200 g.) in xylene (1500 c.c., dried over sodium) was heated in an oil-bath at 140—150° for 32 hr. whilst a rapid stream of carbon dioxide was bubbled through. During the first 10 hr. of this period, sodium (85 g.) was added in small pieces, and more xylene (in all *ca.* 1 l.) was added from time to time to keep the volume constant. Sodium was destroyed in the cooled mixture by the addition of 90% ethanol (*ca.* 480 c.c.), the mixture shaken with water (1600 c.c.), and the aqueous layer acidified. The precipitated acid was collected, washed, and crystallised from a mixture of ethanol (720 c.c.) and water (900 c.c.) (charcoal), giving 2-hydroxy-3 : 6-dimethylbenzoic acid as faintly coloured needles, m. p. 195° (71 g., 24%) (Stollé and Knebel, *loc. cit.*, give m. p. 195°) (Found: equiv., 167. Calc. for $C_8H_9O{\cdot}CO_2H$: equiv., 166). 2 : 5-Dimethylphenol (53 g.) was recovered from the xylene solution.

Di- and Tri-(3 : 6-dimethylsalicylide) (II and III; R = R′ = Me).—2-Hydroxy-3 : 6-dimethylbenzoic acid (20 g.), redistilled phosphorus oxychloride (37 g.), and xylene (120 c.c.) were heated on the water-bath for 12 hr., water (200 c.c.) was added, and the mixture shaken. The solid (A) was collected, washed, and dried (11·0 g.; m. p. 235—241°), and after 2 days the xylene filtrate had deposited a solid (B) (2·0 g.; m. p. 182—206°). The xylene was finally washed with 3% aqueous sodium carbonate, dried, evaporated under reduced pressure, and treated with warm ethanol, giving a solid (C) (0·6 g.; m. p. 222—238°); the alcoholic filtrate was evaporated, and the residue crystallised from light petroleum (b. p. 80—100°), giving solid (D) (0·3 g.; m. p. 201—209°). Solids (A), (B), and (C) were separately crystallised from benzene–light petroleum (b. p. 80—100°), and solid (D) from ethanol. *Tri-(3 : 6-dimethylsalicylide)* (III; R = R′ = Me) was obtained from (A) and (C) as fine needles (9·0 g.), m. p. 254—255° (Found: C, 73·2; H, 5·1%; *M*, 440. $C_{27}H_{24}O_6$ requires C, 73·0; H, 5·4%; *M*, 444). From ethanol, chloroform, or dioxan it crystallises as platelets or needles, m. p. 255°. After melting or crystallisation from benzene and either sublimed at 200°/10^{-4} mm. or heated at 160°/0·5—1 mm., its m. p. was 290—291° (Found: C, 73·2; H, 5·4%) but, on keeping, the m. p. reverted to 255°. Curiously, the m. p. of the material crystallised from ethanol was not affected by heating at 160°/0·5—1 mm. *Di-(3 : 6-dimethylsalicylide)* (II; R = R′ = Me) was obtained from (B) and (D) as hexagonal prisms (1·5 g.), m. p. 211—212° (Found: C, 73·2; H, 5·4%; *M*, 292. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%; *M*, 296). Distillation of the *O*-acetyl derivative of 3 : 6-dimethylsalicylic acid, as described for 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid (p. 2045), gave di-(3 : 6-dimethylsalicylide) in 33% yield.

Hydrolysis of di-(3 : 6-dimethylsalicylide) with boiling 2N-aqueous sodium hydroxide for 6 hr., or of tri-(3 : 6-dimethylsalicylide) with boiling ethanolic potassium hydroxide for 4 hr., gave 2-hydroxy-3 : 6-dimethylbenzoic acid in 86% and 92% yields, respectively. When the two salicylides (0·5 g.) were each boiled for 1 hr. with benzylamine (3 c.c.) and ammonium chloride (0·1 g.), the mixtures treated with dilute hydrochloric acid, and the solids recrystallised 5 times from dilute ethanol, N-*benzyl-2-hydroxy-3 : 6-dimethylbenzamide* was obtained

as needles, m. p. 97—98° (Found: C, 75·2; H, 6·4; N, 5·2. $C_{16}H_{17}O_2N$ requires C, 75·4; H, 6·7; N, 5·5%), in 94% and 78% yield, respectively.

Tetra-(3-phenylsalicylide) (IV; R = Ph, R′ = H).—Technical 3-phenylsalicylic acid (I; R = Ph, R′ = H) (20 g.), distilled phosphorus oxychloride (40 c.c.), and toluene (200 c.c.) were heated on the steam-bath for 40 hr., during which large crystals slowly separated. These were washed with benzene, then with water, and dried (6·1 g., 33%). *Tetra-(3-phenylsalicylide)* (IV; R = Ph, R′ = H) separates from benzene, or from chloroform–light petroleum (b. p. 60—80°) in plates, m. p. 360° [Found: C, 80·0; H, 4·1%; *M*(ebullioscopic in benzene), 731; *M*(ebullioscopic in chloroform), 802. $C_{52}H_{32}O_8$ requires C, 79·6; H, 4·1%; *M*, 784]. The toluene solution contained 3-phenylsalicylic acid and polymeric material.

2-tert.-*Butyl-5-methylphenol* (tert.-*Butyl*-m-*cresol*).—*From* m-*cresol*, tert.-*butyl alcohol, and ferric chloride* (cf. Nazarova and Tsukervanick, *loc. cit.*). Anhydrous ferric chloride (150 g.) was slowly added to *tert.*-butyl alcohol (125 g.) with stirring and cooling, followed by *m*-cresol (110 g.). After 4 days at room temperature, the mixture was poured into water and steam-distilled. A first portion of the distillate (500 c.c.) gave *m*-cresol (24 g.), and the organic layer from the later distillate (3 l.) was separated, dried in ethereal solution ($MgSO_4$), and fractionated in a lagged column, giving *m*-cresol (6 g.; b. p. 105—107°/35 mm.) and 2-*tert.*-butyl-5-methylphenol (60 g.; b. p. 130—135°/35 mm.) (later portions of the steam-distillate contained only material of higher b. p.). The 2-*tert.*-butyl-5-methylphenol was added to stirred, cooled water, giving needles of the hydrate which were dried in a current of air. This product was now dried ($MgSO_4$) in ethereal solution and distilled, giving the free 2-*tert.*-butyl-5-methylphenol, b. p. 130°/13 mm., which solidified on cooling as needles, m. p. 23° (Found: C, 80·7; H, 9·9. Calc. for $C_{11}H_{16}O$: C, 80·5; H, 9·8%). The *hydrate*, prepared from the purified compound, had m. p. 37° [Found: C, 77·6; H, 9·8. $(C_{11}H_{16}O)_3,H_2O$ requires C, 77·6; H, 9·8%. $(C_{11}H_{16}O)_4,H_2O$ requires C, 78·3; H, 9·8%].

2-tert.-*Butyl-6-hydroxy-5-methylbenzoic acid* (3-tert.-*Butyl-6-methylsalicylic Acid*) (I; R = Bu^t, R′ = Me) (cf. Lespagnol and Bar, *loc. cit.*).—To 2-*tert.*-butyl-5-methylphenol (100 g.) in xylene (2 l.) was added sodium (30 g.) in portions with stirring, and the resulting solution heated to boiling (oil-bath) while a vigorous current of carbon dioxide was passed in through two tubes, so as to cause maximum turbulence of the rapidly stirred mixture. This was continued without stoppage for 5 days, xylene (1 l.) removed by distillation, and ethanol (100 c.c.) added to react with any sodium, followed after several hours by shaking with water (1 l.). The aqueous layer and aqueous washings of the xylene layer were acidified, and the solid was collected, dried, and crystallised from light petroleum (b. p. 80—100°) (charcoal), giving finally 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid as colourless needles (110 g., 85%), m. p. 180° (Found: C, 68·9; H, 7·7%; equiv., 203. Calc. for $C_{11}H_{15}O{\cdot}CO_2H$: C, 69·2; H, 7·7%; equiv., 208). This acid gives with alcoholic ferric chloride a deep green colour which changes to blue on addition of water. 6-Acetoxy-2-*tert.*-butyl-5-methylbenzoic acid was obtained by boiling the acid with excess of acetic anhydride and a trace of pyridine for 2 hr., then shaking with much water, and the product which finally solidified was dissolved in cold carbon tetrachloride, and light petroleum (b. p. 40—60°) added till a slight turbidity was produced. After several days, the solid was collected and recrystallised in the same manner, giving the acetyl derivative as needles, m. p. 112° (Lespagnol and Bar gave m. p. 108°).

Di-(3-tert.-butyl-6-methylsalicylide) (II; R = Bu^t, R′ = Me).—The thermal decomposition of 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid was carried out in the apparatus described in Part II (*loc. cit.*, p. 206).

The acid (20 g.) was distilled at 15 mm., the temperature being gradually raised to 350°. Acetic acid was evolved at 120—160°, and a yellowish oil solidifying to a glass was collected mainly at 240—260°. This was dissolved in chloroform, the solution washed with aqueous sodium carbonate, and dried, the chloroform removed, and the residue crystallised from alcohol (yield 5 g., 28%; m. p. 238°), and then from benzene, giving *di-(3-tert.-butyl-6-methylsalicylide)* as needles, m. p. 238° (Found: C, 75·6; H, 7·1%; *M*, 388. $C_{24}H_{28}O_4$ requires C, 75·8; H, 7·4%; *M*, 380). This compound was also obtained as the only anhydro-derivative by dehydration of the acid with either phosphorus oxychloride in xylene (cf. dehydration of 2-hydroxy-3 : 6-dimethylbenzoic acid, p. 2044) (yield 16%) or phosphoric anhydride in xylene (cf. dehydration of *o*-thymotic acid, Baker, Gilbert, and Ollis, Part VI, *J.*, 1952, 1444) (yield, 20%). Hydrolysis by boiling with 50% ethanolic potassium hydroxide for 20 hr. gave 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid, m. p. 180°, in 94% yield.

2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid* (o-*Carvacrotic Acid*) (3-*Methyl*-6-iso*propylsalicylic Acid*) (I; R = Me, R′ = Pr^i).—This acid had been prepared by Kolbe's method in un-

stated yield (Kekulé and Fleischer, *Ber.*, 1873, **6**, 1089; Lustig, *Ber.*, 1886, **19**, 18). It has now been prepared from carvacrol (100 g.) exactly as described above in the case of 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid, the crude product being treated with charcoal in boiling alcohol, and then crystallised from light petroleum (b. p. 80—100°), giving the pure acid as needles, m. p. 140° (103 g., 80%). This acid yielded 2-*acetoxy*-3-*methyl*-6-iso*propylbenzoic acid* when boiled for 2 hr. with acetic anhydride and a little pyridine; it separated from ethanol on cautious addition of water at room temperature as needles, m. p. 131° (Found: C, 66·4; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

Action of Heat on 2-*Acetoxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di*-(3-*methyl*-6-iso*propylsalicylide*) (II; R = Me, R′ = Pr^i).—The acetoxy-derivative (1·4 g.) was distilled at 15 mm. as described above for 6-acetoxy-2-*tert.*-butyl-5-methylbenzoic acid. Acetic acid was evolved at 120—140°, and a thick oil at 300—320° which solidified to a glass. This product was shaken in chloroform solution with aqueous sodium carbonate, the solution dried and evaporated, and the residue crystallised from ethanol, giving *di*-(3-*methyl*-6-iso*propylsalicylide*) (0·4 g., 32%) as needles, m. p. 174° (Found: C, 75·1; H, 6·8%; *M*, 340. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8%; *M*, 352).

Action of Phosphorus Oxychloride on 2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di- and Tri*-(3-*methyl*-6-iso*propylsalicylide*) (II and III; R = Me, R′ = Pr^i).—Phosphorus oxychloride (10 c.c.) was added to a solution of the acid (17 g.) in xylene (100 c.c.), and the mixture boiled for 24 hr., cooled, poured into ice, and well shaken. The xylene layer was shaken with aqueous sodium carbonate, dried, and distilled under reduced pressure, and the residue crystallised from alcohol, giving octagonal plates (3·5 g., 23%) and needles (1·5 g., 10%) which were separated by hand. The needles, m. p. 174°, were di-(3-methyl-6-*iso*propylsalicylide). The octagonal plates, m. p. 247°, were *tri*-(3-*methyl*-6-iso*propylsalicylide*) (Found: C, 74·8; H, 6·8%; *M*, 534. $C_{33}H_{36}O_6$ requires C, 75·0; H, 6·8%; *M*, 528).

Action of Phosphoric Anhydride on 2-*Hydroxy*-3-*methyl*-6-iso*propylbenzoic Acid: Di-, Tri-, and Tetra*-(3-*methyl*-6-iso*propylsalicylide*) (II, III, and IV; R = Me, R′ = Pr^i).—The acid (15 g.) was boiled for 72 hr. in xylene (115 c.c.) with phosphoric anhydride (15 g.), and the products were isolated and recrystallised as in the preceding paragraph. There were isolated the di- (4·5 g., 33%) and tri- (1·5 g., 11%) anhydro-compounds, and also microscopic needles of the *tetra*-(3-*methyl*-6-iso*propylsalicylide*) (0·15 g., 1%), m. p. 323° (Found: C, 74·9; H, 6·8%; *M*, 656. $C_{44}H_{48}O_8$ requires C, 75·0; H, 6·8%; *M*, 704).

The di-, tri-, and tetra-anhydro-compounds were each hydrolysed with boiling 50% ethanolic potassium hydroxide for 24 hr. The first two gave 2-hydroxy-3-methyl-6-*iso*propylbenzoic acid in 98% yield; the last, owing to its insolubility was partly unchanged, but also gave the same acid.

2-*Hydroxy*-6-*methyl*-4-iso*propylbenzoic Acid* (6-*Methyl*-4-iso*propylsalicylic Acid*) (V).—This acid was prepared from 3-methyl-5-*iso*propylphenol (purified technical material) (100 g.) in the same way as 2-*tert.*-butyl-6-hydroxy-5-methylbenzoic acid was prepared from 2-*tert.*-butyl-5-methylphenol. The *acid* separates from light petroleum (b. p. 80—100°) or very dilute ethanol in needles (110 g., 85%), m. p. 136° (Found: C, 68·4; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). With alcoholic ferric chloride it gives an intense purple-blue colour.

Di-(6-*methyl*-4-iso*propylsalicylide*).—The acid (V) was acetylated with acetic anhydride and pyridine, and the oily acetyl derivative (10 g.) distilled at 15 mm. as described in previous cases. Acetic acid was evolved at a bath temperature of 120—140°, and a thick yellowish oil collected between 300° and 330°. This product was worked up as in the case of the 3-methyl-6-*iso*propyl derivative, and gave *di*-(6-*methyl*-4-iso*propylsalicylide*) (2·9 g., 27%) as needles, m. p. 136° (Found: C, 75·0; H, 6·8%; *M*, 360. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·8%; *M*, 352).

Tri-(6-*methyl*-4-iso*propylsalicylide*).—Dehydration of the acid (V) with either phosphorus oxychloride or phosphoric anhydride in xylene at the b. p. as in previous cases gave from each experiment a 7% yield of *tri*-(6-*methyl*-4-iso*propylsalicylide*), which separated from ethanol as needles, m. p. 191° (Found: C, 75·1; H, 6·8%; *M*, 547. $C_{33}H_{36}O_6$ requires C, 75·0; H, 6·8%; *M*, 528).

Hydrolysis of di- and tri-(6-methyl-4-*iso*propylsalicylide) with 50% ethanolic potassium hydroxide for 24 hr. gave 96% and 90% yields, respectively, of 6-methyl-4-*iso*propylsalicylic acid (V), m. p. 136°.

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The Constituents of High-boiling Petroleum Distillates. Part I. Preliminary Studies.

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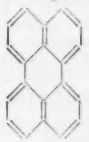
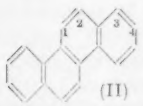
Perylene, an alkylchrysene, and two oxygen-containing compounds have been isolated from an extract of an American crude oil distillate. Several chrysene homologues with large alkyl substituents have been synthesised for comparison with the aforesaid alkylchrysene.

Very little is known about the detailed chemical composition of high-boiling petroleum fractions. It has been established that they consist largely of complex mixtures of hydrocarbons of various types, including aromatic compounds, but in only a few instances have individual components been isolated from them (compare Van Nes and Van Westen, "Aspects of the Constitution of Mineral Oils," Elsevier Publishing Co., Amsterdam, 1951). The aromatic constituents can usually be concentrated by selective extraction from the oil by means of solvents, liquid sulphur dioxide being used industrially for this purpose. We have applied chromatography to several sulphur dioxide extracts which were placed at our disposal. From one of them, prepared from an American petroleum, we have isolated four crystalline compounds. These experiments constitute exploratory work in an investigation sponsored by the Medical Research Council with a view to the identification of carcinogenic components of mineral oils. The experience gained will be applied in the systematic examination of carcinogenic fractions which have been accumulated in a carefully planned fractional distillation of three selected crude oils, each fraction having been submitted to biological test.

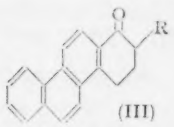
One of the crystalline substances isolated from the extract was a yellow substance $C_{20}H_{12}$, identified as perylene (I) by comparison with an authentic specimen and by its ultra-violet absorption spectrum (Clar, *Ber.*, 1932, **65**, 848).



(I)



(II)



(III)

A second compound, $C_{25}H_{24}$ or $C_{26}H_{26}$, was shown by its ultra-violet absorption spectrum (Fig. 1) to be a derivative of chrysene $C_{18}H_{12}$ (II). It must therefore carry substituents totalling seven or eight carbon atoms, and incorporating a double bond or a ring. Since the compound did not absorb hydrogen in presence of palladium-charcoal and was recovered from attempted dehydrogenation with palladium-black at 300°, it seems probable that the structure includes a ring in a side chain or a five-membered ring fused to the chrysene nucleus. It has not been possible to distinguish between these alternatives.

Attempts to establish the number and orientation of substituents by degradative experiments were unsuccessful. Oxidation with sodium dichromate in acetic acid yielded a mixture of quinones which was converted into an inseparable mixture of acids by further treatment with alkaline hydrogen peroxide. Reaction with alkaline potassium permanganate and with dilute nitric acid likewise led to mixtures of acidic products. Other experiments with *N*-bromosuccinimide, lead tetra-acetate, and selenium dioxide gave no useful result.

For comparative purposes a number of chrysene derivatives with large alkyl groups was synthesised (see Table). These were generally much lower melting than the hydrocarbon from the oil, only those with the substituent at position 4 having comparable melting points. Comparison of the ultra-violet spectra of these compounds with that of the unknown hydrocarbon suggests that the latter is probably a di-, or possibly a tri-substituted chrysene. The position of the substituents is difficult to decide from the spectrum, but it seems likely

that no substituent is present at positions 1, 6, 7, or 12 (compare Brode and Patterson, *J. Amer. Chem. Soc.*, 1941, **63**, 3252). It is of interest that another chrysene derivative, 3-methylchrysene, has recently been isolated from a fraction of an American crude oil (Moore, Thorpe, and Mahoney, *ibid.*, 1953, **75**, 2259).

FIG. 1.

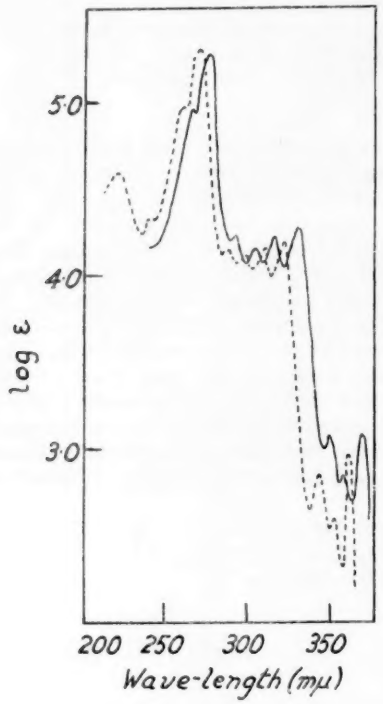
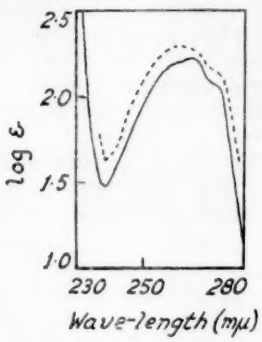


FIG. 1. *Ultra-violet absorption spectrum of hydrocarbon from mineral oil* (——) *and of chrysene* (– – – –) *in* 95% *ethanol.*

FIG. 2. *Ultra-violet absorption spectrum of compound from oil* (——) *and of* 1 : 2 : 3 : 4-*tetrahydro*-5-*methylnaphthalene* (– – – –) (Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," John Wiley & Sons, New York, 1951).



Compound	M. p.		Ultra-violet absorption maxima (mμ) *								
Chrysene	256°	λ	258	267	282	293	305	319	343	351	360
		log ε	4·96	5·20	4·09	4·09	4·13	4·13	2·81	2·51	2·81
Hydrocarbon from oil	247	λ	265	274	—	301	314	327·5	348·5	354	367
		log ε	4·87	5·09	—	4·09	4·17	4·17	2·82	2·62	2·83
2-*n*-Heptylchrysene	83—84	λ	261	270·5	—	299	311·5	326	347	—	365
		log ε	4·86	5·10	—	4·01	4·15	4·15	3·03	—	2·92
3-*n*-Heptylchrysene	127	λ	261	270·5	—	299	311	325	346	352·5	364
		log ε	4·93	5·15	—	4·08	4·17	4·14	2·87	2·65	2·75
4-*n*-Heptylchrysene	174	λ	261	271	(285)	296	308	321	345	352	363
		log ε	4·91	5·19	(4·21)	4·17	4·12	4·07	2·68	2·51	2·51
4-*cyclo*Hexylmethylchrysene	203—204	λ	262	271·5	—	(296)	308	321	345·5	353	363
		log ε	4·76	5·03	—	(4·17)	4·04	3·96	2·54	2·40	2·24
5-*n*-Heptylchrysene	91	λ	262	271	(285)	296·5	308·5	322	347	355	364
		log ε	4·84	5·08	(4·14)	4·07	4·09	4·09	2·88	2·55	2·88
5-*cyclo*Hexylmethylchrysene	138—139	λ	261·5	271	—	297	309	322	346·5	354	364
		log ε	4·96	5·20	—	4·09	4·11	4·11	3·86	2·55	2·77
3-*n*-Hexyl-4-methylchrysene	141	λ	263·5	272·5	—	300	313	325·5	347	354	365
		log ε	4·84	5·08	—	4·08	4·09	4·05	2·85	2·61	2·57

* Figures in parentheses indicate inflexions.

Another compound, isolated in very small amount, had the molecular formula $C_{20}H_{28}O$, $C_{21}H_{30}O$, or $C_{22}H_{32}O$. It was unaffected by hot dilute acid or alkali, and did not react with 2 : 4-dinitrophenylhydrazine sulphate in ethanol, or with *p*-nitrobenzoyl chloride. It did not decolorise bromine in carbon tetrachloride, but micro-hydrogenation with platinum in acetic acid showed the presence of three double bonds. These are attributed to the presence

of a benzene ring, and this view is supported by the ultra-violet absorption spectrum (Fig. 2) which is similar to that of typical alkylbenzenes. The compound was recovered from attempted dehydrogenation with palladium at 300°. The absence of hydroxyl and carbonyl functions was confirmed by the infra-red spectrum, which showed no absorption in the characteristic carbonyl- and hydroxyl-stretching regions. The evidence available suggests a tetracyclic structure, one of the rings being benzenoid and the others alicyclic. The oxygen is probably present as an ether grouping, but an attempt to demonstrate this by treatment with hydriodic acid yielded a gummy product.

The fourth compound also appeared to be largely non-aromatic. Elementary analysis could not distinguish between the formulæ $C_{27}H_{42}O_2$, $C_{28}H_{44}O_2$, $C_{29}H_{46}O_2$, and $C_{30}H_{48}O_2$. It was unchanged by boiling dilute aqueous or alcoholic acid or alkali, and did not react with 2 : 4-dinitrophenylhydrazine sulphate or with 3 : 5-dinitrobenzoyl chloride. The infra-red spectrum showed no hydroxyl absorption but, surprisingly, exhibited a very distinct band at a typical carbonyl frequency (1756 $\pm$ 5 cm.$^{-1}$), attributable to carbonyl in a ring or to an ester or, less likely, a carboxyl group (compare Jones, Williams, Whallon, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024). None of these groups could be detected by chemical means. Carbonyl, if present, must be highly hindered, for the compound did not react with hydroxylamine even in boiling diethylene glycol. Attempts to dehydrogenate the compound with palladium or selenium at 300° were unsuccessful. At higher temperatures with selenium the substance was decomposed but no aromatic compound could be isolated from the product. Attempted reduction with phosphorus and hydriodic acid led to resinous products.

The alkylchrysenes listed in the Table were prepared by standard methods. Reaction of 3 : 4 : 5 : 6-tetrahydro-3-oxochrysene (III; R = H) (Bachmann and Struve, *J. Org. Chem.*, 1940, **5**, 416) with *n*-heptylmagnesium bromide yielded a tertiary alcohol and hence, by heating with palladium, 3-*n*-heptylchrysene (cf. *idem*, *ibid.*, 1939, **4**, 456). 3-*n*-Hexyl-4-methylchrysene was similarly obtained from 3 : 4 : 5 : 6-tetrahydro-4-methyl-3-oxochrysene (III; R = Me) and *n*-hexylmagnesium bromide. The other hydrocarbons were obtained by Clemmensen reduction of the corresponding ketones prepared from chrysene by Friedel–Crafts reaction with *n*-heptanoyl and *cyclo*hexanecarbonyl chloride (compare Carruthers, *J.*, 1953, 3486). Thus reaction of chrysene with *n*-heptanoyl chloride and aluminium chloride in nitrobenzene gave a mixture of products from which 4- and 5-*n*-heptanoylchrysenes were isolated; 2-*n*-heptanoylchrysene was obtained when the reaction was conducted in methylene chloride. The orientation of these ketones was confirmed by oxidation to the known chrysenecarboxylic acids, and is similar to that obtaining in the Friedel–Crafts acetylation of chrysene (Carruthers, *loc. cit.*). 4- and 5-*cyclo*Hexanecarbonylchrysenes similarly resulted from reaction of chrysene with aluminium chloride and *cyclo*hexanecarbonyl chloride in nitrobenzene solution. They were converted into the chrysenecarboxylic acids, and thus orientated, by reduction with lithium aluminium hydride, dehydration of the resulting alcohols by means of potassium hydrogen sulphate, and oxidation of the products with potassium permanganate in acetone.

Experimental

Absorption spectra were determined in 95% ethanol with a " Unicam " spectrophotometer. Unless otherwise stated, " light petroleum " refers to the fraction of b. p. 60—80°.

Chromatography of the Extract.—The extract was a dark, very viscous oil at ordinary temperatures, prepared commercially by treatment of a lubricating-oil fraction of a West Baumont, U.S.A., crude with liquid sulphur dioxide. It was supplied by Manchester Oil Refinery and had been found by Dr. D. L. Woodhouse, of the University of Birmingham, to be non-carcinogenic. The material was distilled at 220—240°/4·7 $\times$ 10^{-3} mm. (air-bath temp.), yielding a viscous orange-red distillate.

In a typical experiment the distillate (30 g.) was chromatographed on alumina (800 g.) from solution in light petroleum (b. p. 40—60°; 300 c.c.). The column was eluted with light petroleum (b. p. 40—60°) until no more material came through (2 l.). Evaporation of the eluate yielded a nearly colourless oil (20 g.). Development was continued with benzene–light petroleum (1 : 1; 250 c.c.), benzene–light petroleum (3 : 1; 500 c.c.), and benzene (250 c.c.), and the eluate collected

in fractions of 50 c.c. Concentration of these afforded dark gums, some of which yielded crystalline compounds as described below.

Chrysene Derivative.—Several of the early benzene–light petroleum fractions (4—7) deposited small amounts of a yellow solid when triturated with light petroleum (b. p. 40—60°) at 0°. This was collected (40 mg.) and purified by crystallisation of its molecular complex with 2 : 4 : 7-trinitrofluorenone, from which it was recovered by treatment with stannous chloride in boiling acetic acid. It crystallised from benzene in colourless plates, m. p. 247—248° (Found : C, 92·4; 92·6; H, 7·6, 7·4. Calc. for $C_{25}H_{24}$: C, 92·6; H, 7·4%. Calc. for $C_{26}H_{26}$: C, 92·3; H, 7·7%). Ultra-violet absorption data are recorded in the Table. The 2 : 4 : 7-trinitrofluorenone complex formed fine brick-red needles from toluene, m. p. 258—259° (Found : C, 71·2; H, 4·5; N, 6·5. Calc. for $C_{38}H_{29}O_7N_3$: C, 71·4; H, 4·5; N, 6·6%. Calc. for $C_{39}H_{31}O_7N_3$: C, 71·7; H, 4·8; N, 6·4%). The 2 : 7-dinitroanthraquinone complex gave fine, bright red needles from benzene, m. p. 260° (decomp.) (Found : C, 75·4; H, 5·0; N, 4·6. Calc. for $C_{39}H_{30}O_6N_2$: C, 75·2; H, 4·8; N, 4·5%. Calc. for $C_{40}H_{32}O_6N_2$: C, 75·5; H, 5·0; N, 4·4%).

Perylene.—The gums from which the above hydrocarbon had been obtained, accumulated from a number of chromatograms, were collected (26 g.) and chromatographed on alumina in benzene solution. Fifteen arbitrary fractions of 30 c.c. were collected. Evaporation yielded gums, some of which deposited crystals of the above hydrocarbon (300 mg.) after some time. From several of the fractions immediately following, a yellow compound (64 mg.) was obtained on trituration with light petroleum. After further purification by repeated chromatography on alumina in benzene, and by crystallisation of its molecular complex with *s*-trinitrobenzene, it formed golden-yellow plates (from benzene), m. p. 268—269° alone or mixed with synthetic perylene (Found : C, 94·9; H, 4·8. Calc. for $C_{20}H_{12}$: C, 95·2; H, 4·8%). Light absorption in ethanol : $\lambda_{max.}$ 245, 252, 263, 286, 291, 300, 323, 328, 338, 367, 387, 408, 436 mμ. With concentrated sulphuric acid the hydrocarbon gave a transient green followed by a stable purple colour. The picrate formed brown needles (from benzene), m. p. 219—222° not lowered on admixture with perylene monopicrate (Brass and Tingler, *Ber.*, 1931, **64**, 1650). The *s*-trinitrobenzene complex crystallised from benzene in deep red needles, m. p. 244°. The *s*-trinitrobenzene complex of perylene is described by Hertel and Bergck (*Z. physikal. Chem.*, 1936, **33**, *B*, 324) as black needles, m. p. 276°. However, a sample prepared from pure perylene in benzene formed deep red needles, m. p. 246°, and was identical with the compound described above (mixed m. p.) (Found : C, 67·3; H, 3·3; N, 9·3. Calc. for $C_{26}H_{15}O_6N_3$: C, 67·1; H, 3·2; N, 9·0%).

The Oxygen-containing Compounds.—The gums recovered from the later benzene–light petroleum and benzene eluates of the chromatograms sometimes deposited crystals after a long time. These were collected and separately crystallised. By this means two homogeneous compounds were obtained. (*a*) One was readily purified by crystallisation from benzene, from which it crystallised in colourless plates, m. p. 252—253° (170 mg. from several experiments). Halogens, nitrogen, and sulphur were absent (Found : C, 84·5, 84·2; H, 10·3, 10·2. Calc. for $C_{20}H_{28}O$: C, 84·5; H, 9·9%. Calc. for $C_{21}H_{30}O$: C, 84·6; H, 10·1%. Calc. for $C_{22}H_{32}O$: C, 84·6; H, 10·3%). (*b*) The other compound was more difficult to purify. The crude material (670 mg.) was crystallised several times from acetic acid and from benzene, and then formed colourless needles, m. p. 290—300° depending on the rate of heating. Careful chromatography of this material on alumina in benzene, followed by sublimation at 300°/20 mm., afforded crystals with the same properties. By repeated crystallisation from benzene, colourless needles were obtained which melted at 330° (decomp.) (bath preheated to 300°). Sulphur, halogens, and nitrogen were absent [Found : C, 81·8, 81·6; H, 10·7, 10·8%; *M* (Rast), 370. Calc. for $C_{27}H_{42}O_2$: C, 81·4; H, 10·6%; *M*, 398. Calc. for $C_{28}H_{44}O_2$: C, 81·6; H, 10·7%. Calc. for $C_{29}H_{46}O_2$: C, 81·7; H, 10·8%. Calc. for $C_{30}H_{48}O_2$: C, 81·9; H, 10·9%].

4- *and* 5-n-*Heptanoylchrysene.*—A suspension of finely powdered chrysene (9 g.) in nitrobenzene (50 c.c.) was added with stirring to an ice-cold solution of aluminium chloride (6 g.) and *n*-heptanoyl chloride (6·7 g.) in nitrobenzene (30 c.c.). After 1 hr. the temperature was raised to 35—40° for 5 hr. Next morning, ice and hydrochloric acid were added, and nitrobenzene was removed in steam. The product (9 g.) was collected and extracted with boiling ethanol (4 × 100 c.c.), and the residue (6 g.) distilled at 210°/10^{-2} mm. The distillate was chromatographed on alumina in benzene solution. After removal of chrysene (0·8 g.) a ketonic product was recovered. This was dissolved in carbon tetrachloride (100 c.c.), and the solution set aside. The crystals (1·4 g.) which separated were crystallised further from carbon tetrachloride and from benzene, 4-n-*heptanoylchrysene* (0·4 g.) being obtained as colourless needles which collapsed to an opaque liquid at 187° and finally melted at 198—199°. Repeated crystallisation of this

material from different solvents, and careful chromatography on alumina did not lead to any sharper definition of the m. p. (Found: C, 87·9; H, 7·2. $C_{25}H_{24}O$ requires C, 88·2; H, 7·1%). Oxidation with potassium hypoiodite in aqueous dioxan (Fuson and Tulloch, *J. Amer. Chem. Soc.*, 1934, **56**, 1638) afforded chrysene-4-carboxylic acid, m. p. 317—318° (decomp.); the methyl ester formed pale yellow plates in benzene, m. p. 218—220° alone or mixed with an authentic specimen.

The carbon tetrachloride mother-liquors were concentrated to 30 c.c. After removal of some 4-*n*-heptanoylchrysene (0·2 g.) the solution was set aside at 0° for several days. The crystals (1·2 g.) which separated were collected. Crystallisation from benzene–ethanol afforded 5-n-*heptanoylchrysene* as colourless needles, m. p. 96—97° (Found: C, 88·0; H, 7·0%). Oxidation of this compound as described above gave chrysene-5-carboxylic acid, m. p. 295° (decomp.); methyl ester, m. p. 147—148° alone or mixed with an authentic specimen.

2-n-*Heptanoylchrysene.*—Chrysene (4 g.) was added to a stirred ice-cold solution of aluminium chloride (2·9 g.) and *n*-heptanoyl chloride (3 g.) in methylene chloride (30 c.c.). Next morning stirring was continued for 2 hr. at 35—40°. Ice and hydrochloric acid were added, and methylene chloride distilled off. The dark gum was dissolved in benzene, a small amount of insoluble material filtered off, and the solution chromatographed on alumina. Elution with benzene–light petroleum (1 : 1) removed first some chrysene (0·5 g.), then a yellow gum (2·6 g.) which crystallised on trituration with ethanol. Crystallisation from ethanol gave colourless needles of 2-n-*heptanoylchrysene*, m. p. 66° (Found: C, 88·0; H, 7·1%). Oxidation of this ketone by the method of Arnold and Rondesvedt (*J. Amer. Chem. Soc.*, 1945, **67**, 1265) with selenium dioxide followed by alkaline hydrogen peroxide yielded chrysene-2-carboxylic acid, m. p. 300° (decomp.) (methyl ester, m. p. 141—142° not reduced when mixed with an authentic specimen).

4- *and* 5-cyclo*Hexanecarbonylchrysene.*—Finely powdered chrysene (11 g.) with nitrobenzene (20 c.c.) was added to a stirred solution of aluminium chloride (7·5 g.) and *cyclo*hexanecarbonyl chloride (8·4 g.) in nitrobenzene (30 c.c.) at 0°. After 1½ hr. the temperature was raised to 35—40° for 4 hr. Next morning, ice and hydrochloric acid were added, and nitrobenzene was removed in steam. The solid residue was powdered, washed, dried, and extracted with boiling carbon tetrachloride (100 c.c.), and the solution set aside. The solid which separated was combined with the insoluble residue, and the whole chromatographed in benzene on alumina. After removal of chrysene (0·3 g.), 4-cyclo*hexanecarbonylchrysene* (1·3 g.) was recovered, and crystallised from benzene in colourless needles, m. p. 211—212° (Found: C, 88·8; H, 6·7. $C_{25}H_{22}O$ requires C, 88·8; H, 6·6%). The carbon tetrachloride mother-liquors were concentrated to 20 c.c. and set aside at 0° for several days. The dark solid (7·9 g.) was collected and chromatographed in benzene on alumina to remove chrysene (0·5 g.) as described above. The recovered ketonic product was crystallised from carbon tetrachloride (30 c.c.). After removal of some of the 4-isomer (0·6 g.), 5-cyclo*hexanecarbonylchrysene* (2·9 g.) was obtained. It formed colourless blades, m. p. 168—169°, from benzene–*cyclo*hexane (Found: C, 88·7; H, 6·4%).

Treatment of the 4-isomer (150 mg.) with excess of lithium aluminium hydride in ether afforded an alcohol, m. p. 220—221°. This was dehydrated with potassium hydrogen sulphate (100 mg.) at 160° for ½ hr. The resulting olefin was purified by chromatography on alumina, and formed colourless crystals, m. p. 94—197°. It was oxidised with potassium permanganate (0·5 g.) in acetone (50 c.c.) at 20° for 12 hr. After evaporation of acetone, and removal of manganese dioxide with aqueous sulphurous acid, a product was obtained which yielded an acid (15 mg.) on extraction with dilute alkali. The acid was converted directly into the methyl ester with diazomethane. Crystallisation from methanol (charcoal) gave crystals of methyl chrysene-4-carboxylate, m. p. 214—215°, identified by comparison with an authentic specimen.

Methyl chrysene-5-carboxylate, m. p. 144—145°, was similarly obtained from 5-*cyclo*hexanecarbonylchrysene, *via* the olefin, m. p. 114—117°.

2-n-*Heptylchrysene.*—A mixture of 2-*n*-heptanoylchrysene (0·5 g.), amalgamated zinc (5 g.), toluene (2 c.c.), ethanol (2 c.c.), and concentrated hydrochloric acid (15 c.c.) was boiled for 24 hr. The oily product was chromatographed on alumina in light petroleum, and afforded 2-n-*heptylchrysene* (0·3 g.) as colourless needles, m. p. 83—84° (from *cyclo*hexane) (Found: C, 91·8; H, 7·9. $C_{25}H_{26}$ requires C, 92·0; H, 8·0%). The *s*-trinitrobenzene *complex* formed deep yellow needles, m. p. 125°, from ethanol (Found: N, 8·0. $C_{31}H_{29}O_6N_3$ requires N, 7·8%).

3-n-*Heptylchrysene.*—To a solution prepared from *n*-heptyl bromide (2 g.) and magnesium (0·35 g.) in ether (10 c.c.) was added 3 : 4 : 5 : 6-tetrahydro-3-oxochrysene (0·4 g.) (Bachmann and Struve, *J. Org. Chem.*, 1940, **5**, 416) in benzene (10 c.c.), and the mixture refluxed for an hour. Next morning the complex was decomposed with dilute sulphuric acid and the oily product

obtained was heated at 180°/15 mm. for a short time to remove some high-boiling liquid. The resulting solid was heated with palladium black (50 mg.) at 280—290° for an hour in an atmosphere of carbon dioxide. The product was extracted with benzene, and purified by chromatography on alumina, and by sublimation at 200°/0·5 mm. 3-n-*Heptylchrysene* (360 mg.) was obtained as colourless needles, m. p. 127° (from ethanol) (Found: C, 91·9; H, 8·1%). The 2 : 4 : 7-trinitrofluorenone complex formed brick-red micro-crystals (from benzene), m. p. 175°, but could not be obtained free from the fluorenone (Found: N, 7·3. Calc. for $C_{38}H_{31}O_7N_3$: N, 6·5%). The picrate, and the complexes with *s*-trinitrobenzene and 2 : 7-dinitroanthraquinone, showed more pronounced dissociation on crystallisation.

3-n-*Hexyl*-4-*methylchrysene*.—A solution of 3 : 4 : 5 : 6-tetrahydro-4-methyl-3-oxochrysene (Bachmann and Struve, *loc. cit.*) (130 mg.) in benzene (10 c.c.) was added to a solution prepared from *n*-hexyl bromide (1·5 g.) and magnesium (0·27 g.) in ether (6 c.c.), and the mixture boiled for ½ hr. Next morning, dilute sulphuric acid was added, and the product recovered in the usual way. Some high-boiling liquid was distilled off at 180°/0·5 mm., and the residue heated with palladium–charcoal (30%; 300 mg.) at 290—300° for an hour in an atmosphere of carbon dioxide. The product (100 mg.) was purified by chromatography on alumina in benzene. 3-n-*Hexyl*-4-*methylchrysene* was obtained as colourless plates, from m. p. 141°, ethanol–benzene (Found: C, 91·8; H, 7·9%). The molecular complexes with *s*-trinitrobenzene, 2 : 7-dinitroanthraquinone, and 2 : 4 : 7-trinitrofluorenone dissociated on crystallisation; the last formed orange-red microcrystals (from benzene), m. p. 208° (Found: N, 7·4%).

4-n-*Heptylchrysene*.—A mixture of 4-*n*-heptanoylchrysene (400 mg.), amalgamated zinc (8 g.), toluene (2 c.c.), acetic acid (2 c.c.), and hydrochloric acid (10 c.c.) was boiled for 30 hr. The product was purified by chromatography on alumina in benzene–light petroleum (1 : 10), and 4-n-*heptylchrysene* (75 mg.) obtained as colourless plates, m. p. 174° (from ethanol–benzene) (Found: C, 92·0; H, 8·1%). The 2 : 7-dinitroanthraquinone complex formed bright red crystals, m. p. 222°, but dissociated on crystallisation. The 2 : 4 : 7-trinitrofluorenone and *s*-trinitrobenzene complexes behaved likewise.

5-n-*Heptylchrysene*.—This was prepared from 5-*n*-heptanoylchrysene (400 mg.) as described for the 4-isomer. After purification by chromatography, 5-n-*heptylchrysene* (300 mg.) crystallised from ethanol in colourless plates, m. p. 91° (Found: C, 91·9; H, 7·9%). The *s*-trinitrobenzene *complex* crystallised in yellow needles, m. p. 102—103° (from ethanol) (Found: N, 7·7. $C_{31}H_{29}O_6N_3$ requires N, 7·8%).

4-cyclo*Hexylmethylchrysene*.—4-*cyclo*Hexanecarbonylchrysene (150 mg.), amalgamated zinc (2 g.), acetic acid (2 c.c.), toluene (2 c.c.), and concentrated hydrochloric acid (10 c.c.) were boiled together for 40 hr. The product (110 mg.) was purified by chromatography on alumina in light petroleum. 4-cyclo*Hexylmethylchrysene* crystallised from *cyclo*hexane–benzene (1 : 1) in colourless plates, m. p. 203—204° (Found: C, 92·5; H, 7·6. $C_{25}H_{24}$ requires C, 92·6; H, 7·5%). The 2 : 7-dinitroanthraquinone *complex* gave bright red plates (from benzene), m. p. 243° (Found: N, 4·5. $C_{39}H_{30}O_6N_2$ requires N, 4·5%).

5-cyclo*Hexylmethylchrysene*.—This was prepared from 5-*cyclo*hexanecarbonylchrysene (200 mg.) as was the 4-isomer. After purification by chromatography in light petroleum on alumina, it formed colourless needles, from *cyclo*hexane, m. p. 138—139° (Found: C, 92·5; H, 7·5%). The *s*-trinitrobenzene *complex* formed yellow needles (from ethanol), m. p. 166° (Found: N, 8·0. $C_{31}H_{27}O_6N_3$ requires N, 7·8%).

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The Decomposition of Silver Oxalate.

By A. Finch, P. W. M. Jacobs, and F. C Tompkins.

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In an attempt to resolve some of the apparent anomalies in previous work on the decomposition of silver oxalate, the ionic and photoconductance of this salt have been measured and the photolysis and thermal decomposition of several different preparations have been investigated. The kinetics of the photolysis are explained by an exciton mechanism similar to, but not identical with, that previously applied to the decomposition of barium and potassium azides. The theory, originally due to Macdonald, that the thermal decomposition of the freshly prepared salt proceeds by a branching-chain mechanism, has been successfully developed to account quantitatively for all features of the thermal decomposition. The role of dislocations in thermal decompositions of this type has been emphasized and some apparent discrepancies between the present and previous work have been reconciled.

The several previous investigations of the thermal decomposition of silver oxalate have given markedly different results, and consequently different interpretations of the kinetics have been proposed. Benton and Cunningham (*J. Amer. Chem. Soc.*, 1935, **57**, 2227) and Tompkins (*Trans. Faraday Soc.*, 1948, **44**, 206) found the pressure of carbon dioxide evolved to vary as the third or fourth power of the time, a result consistent with three-dimensional growth of silver nuclei, whereas Macdonald (*J.*, 1936, 832, 839) concluded that the reaction starts from a fixed number of centres which grow two-dimensionally. Macdonald considered that the plates of silver so formed would branch, and thus accounted for the predominantly exponential character of his pressure–time plots. In later work, however, Macdonald and Sandison (*Trans. Faraday Soc.*, 1938, **34**, 589) showed that ionic conductance measurements favoured the concept of solid nuclei although the p–t plots were again exponential.

The rate of decomposition is sensitive to the method of preparation of the oxalate (Macdonald, *loc. cit.*), that obtained when using excess of oxalate ions during precipitation being of the " unstable accelerating " type, whereas that prepared with use of excess of silver ions is of the " stable, feebly accelerating " type. Consequently, in an attempt to resolve some of these differences, the ionic and photoconductance of silver oxalate, its decomposition at room temperature under ultra-violet radiation, and the thermal decomposition of irradiated and unirradiated salt have been investigated, different preparations being used.

Experimental

Preparation of Silver Oxalate.—Four different preparations were used, viz., (I) a " stoicheiometric " sample, prepared by Tompkins's procedure (*loc. cit.*); (II) an " excess of oxalate " sample prepared in the presence of excess of sodium oxalate; (III) as (II), but with use of oxalic acid; (IV) an " excess of silver " sample. The preparation of (II) and (IV) followed Macdonald's procedure and correspond to his samples C and E.

In the measurements of ionic and photoconductance the apparatus and procedure were similar to those used by Jacobs (*J. Sci. Instr.*, 1953, **30**, 204). The investigation of prolonged photolysis, pre-irradiation, and thermal decomposition followed closely the methods described by Thomas and Tompkins (*J. Chem. Phys.*, 1952, **20**, 662; *Proc. Roy. Soc.*, 1951, *A*, **209**, 550; **210**, 111).

Results and Discussion

The specific ionic conductance κ of compressed pellets of (I) as a function of temperature was found to be well represented by the equation

$$\log \kappa = -6{\cdot}00 - (10{\cdot}7 \text{ kcal.}/2{\cdot}3\boldsymbol{R}T) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The reproducibility of conductance values was $\pm 2\%$ for different pellets of (I) while the values of κ obtained with samples (II), (III), (IV), and (I) after *slight* thermal decomposition at 320° K also obeyed formula (I) within the experimental error. The conductance

(10^{-12} ohm^{-1} cm.$^{-1}$ at 333° K) is thus of a similar order of magnitude to that of barium azide but differs markedly from that of silver chloride and bromide (10^{-7} ohm^{-1} cm.$^{-1}$ at the same temperature). Following Thomas and Tompkins (*Proc. Roy. Soc., loc. cit.*) it is concluded that the mechanism of growth of discrete silver nuclei, involving cationic transport, valid for the silver halides, cannot be applied to the oxalate, in which individual nuclei have never been observed; an interface reaction is, therefore, more probable.

As with barium azide, no photocurrent greater than 10^{-13} A was obtained when the oxalate was illuminated either with a low-pressure argon-filled ultra-violet lamp or with a tungsten lamp. Calculations based on the light intensity (cf. Jacobs and Tompkins, *Proc. Roy. Soc.*, 1952, *A*, **215**, 254) show that any mechanism for photolysis involving conduction electrons cannot be applied and thus an exciton mechanism (cf. Thomas and Tompkins, *loc. cit.*) is probable.

On prolonged photolysis by ultra-violet light (about 90% $\lambda = 2537$ Å) silver oxalate decomposed stoicheiometrically into silver and carbon dioxide. At constant intensity and temperature, the rate of gas evolution was practically constant after an initial, more rapid rate during the first 15 min. when a fresh sample of oxalate was irradiated for the first time.

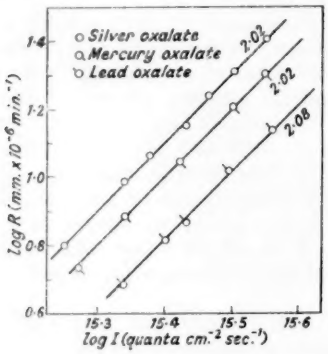


FIG. 1.
Variation of the rate of photolysis with intensity for oxalates of silver, lead, and mercury(II). Values on curve denote value of exponent in $R \propto I^n$.

Gas evolution commenced and ceased immediately on the light's being switched on and off. At constant intensity the linear rate increased slightly with temperature in the range 200—300° K with an activation energy E of 950 cal./mole, which was unaltered by a three-fold increase in the intensity (cf. Tompkins, *loc. cit.*, who found $E = 850$ cal./mole).

At constant temperature, the linear rate R varied as the square of the intensity I; this is shown in Fig. 1, where log R is plotted against log I. The same relation held for the oxalates of lead and mercury(II) (Fig. 1), and also, as found previously, for potassium and barium azides. Tompkins (*loc. cit.*), had obtained a dependence of rate on intensity of the form $R \propto I^{1\cdot7}$; when these results are corrected for the outgassing rate, the square law is found to be obeyed, and particularly well at higher intensities.

The exciton theory, previously given for the photolysis of barium azide, may be applied to that of silver oxalate with little modification. The main difference is that a single oxalate " radical " may decompose to carbon dioxide, whereas with barium azide two excitons, or excited azide ions, are essential for the production of nitrogen according to the equation

$$2[N_3]^- \longrightarrow 3N_2 + 2\text{F-centres}$$

The process that we envisage for silver oxalate is the production of a singly excited oxalate ion (or exciton) by the ultra-violet radiation, such that the excited electron is still associated with the parent ion. The mobile exciton is trapped at an anion vacancy, a process that involves the capture of the excited electron by the vacancy which may accommodate two electrons. The complex formed is analogous to the coloration complex obtained with potassium azide (Jacobs and Tompkins, *loc. cit.*). This complex (i) may either be further excited by light absorption so that a second electron is captured by the anion vacancy, giving an oxalate radical associated with an anion vacancy containing two electrons; or (ii) it may be destroyed by the electron returning by tunnel effect from the anion vacancy

back to the singly-charged ion. Similarly, the oxalate radical formed by (i) may either (iii) decompose to give two molecules of carbon dioxide or (iv) revert to a singly-charged oxalate ion by regaining an electron from the anion vacancy. The possible processes are summarized by the reaction scheme:

$$Ox^{2-} + h\nu \xrightarrow{k_1} [Ox^-]^- \text{ (stabilized exciton)}$$

$$[Ox^-]^- \xrightarrow{k_2} Ox^{2-}$$

$$[Ox^-]^- + h\nu \xrightarrow{k_3} [Ox]^{2-} \text{ (double exciton)}$$

$$[Ox]^{2-} \xrightarrow{k_4} [Ox^-]^-$$

$$[Ox]^{2-} \xrightarrow{k_5} 2CO_2 + [2e^-] \text{ (anion vacancy + two electrons)}$$

Since a steady state is set up, the rate of decomposition R is given by

$$R = k_1k_3k_5NI^2/(k_2 + k_3I)\,(k_4 + k_5) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Here N is the number of anion vacancies per cm.^{2} of surface; k_1, k_3 are the probabilities that the absorption of a quantum will lead to excitation of an oxalate ion adjacent to an anion vacancy; k_2 and k_4 are tunnelling probabilities; and k_5 is the rate constant for the decomposition of complexes. The latter is given by $s\nu e^{-E/RT}$, where s is a steric factor and ν the lattice frequency ($\sim 10^{13}$ sec.$^{-1}$); E, the activation energy for the decomposition of complexes, has the measured value of 950 cal./mole, provided k_2 and k_4 are temperature-independent. Since $R \propto I^2$, it follows that $k_2 > k_3I$, and since there is a single experimental activation energy, $k_4 > k_5$. Equation (2) may, therefore, be put in the approximate form

$$R = k_1k_3k_5NI^2/k_2k_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$
$$= 2{\cdot}9 \times 10^{13}e^{-950/RT}$$

Following Jacobs and Tompkins (*loc. cit.*), we put $k_1I \simeq k_3I \simeq 6 \times 10^8$ sec.$^{-1}$, $k_2 \simeq k_4$, and calculate N from the conductance equation as $1{\cdot}5 \times 10^5$ cm.$^{-2}$. Substitution of these values in equation (3) gives

$$k_2 \simeq k_4 = 1{\cdot}4 \times 10^{11}s^{\frac{1}{2}}$$

But since $k_2 > k_3I$ and $k_4 > k_5$,

$$0{\cdot}043 < s^{\frac{1}{2}} < 0{\cdot}07$$

and therefore

$$s \simeq 3 \times 10^{-4}$$

and

$$k_2 \simeq k_4 \simeq 2{\cdot}5 \times 10^9$$

This value is in fair agreement with that calculated by Jacobs and Tompkins (*Proc. Roy. Soc.*, 1952, *A*, **215**, 265) for the rate of decay of colour centres in potassium azide (5×10^{10}). Thus the theory allows a self-consistent set of the constants appearing in equation (3) to be calculated.

The main objection is that such a low value for s would not be expected for a "unimolecular radical" decomposition at a solid surface. However, this may be accounted for in the following way. Griffith's X-ray work (*J. Chem. Phys.*, 1946, **14**, 403) has shown that silver oxalate possesses a layer lattice, the silver and the oxalate ions occurring in alternate layers with the oxygen atoms in successive oxalate ions co-ordinately bound to one another. It is thus necessary to break more than a single C–C bond to free two molecules of carbon dioxide from the lattice. Nevertheless, the activation energy to do this (~1 kcal.) is small and we would not expect any considerable steric factor to be associated with a disruption requiring so little energy. More probably, k_2 and k_4 are temperature-dependent, *i.e.*, tunnelling only takes place from a thermally excited state within the vacancy. This seems likely from the work of Schneider ("Photographic Sensitivity," Butterworths London, 1951) on the bleaching of coloration complexes in potassium chloride and of Groocock and Tompkins (*Proc. Roy. Soc.*, 1954, *A*, in the press) on the decomposition of barium and sodium azides after electron bombardment. Writing $k_2 \simeq k_4 = \kappa\nu e^{-E'/RT}$ we find that $E \simeq 4{\cdot}5$ kcal. if the transmission coefficient κ is unity. The true activation energy for the decomposition of complexes is thus about 10 kcal. and the low steric factor found is thus reasonable.

The Thermal Decomposition.—The thermal decomposition of all four preparations was investigated between 105° and 120° C, in which temperature range self-heating is negligible (Macdonald, *loc. cit.*). All the pressure–time curves obtained were well represented from $\alpha = 0{\cdot}05\%$ decomposition to at least 30% by the equation

$$p = Ce^{kt}. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

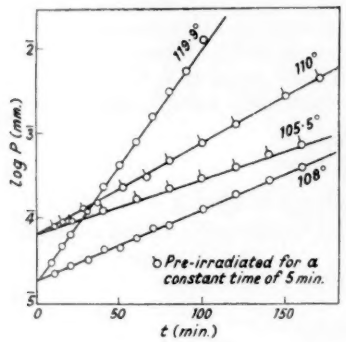
where C and k are constants. Typical plots of log p against t are given in Fig. 2, and plots of log k against $1/T$ for various preparations are shown in Fig. 3. Values of k were consistently reproducible to $\pm 2\%$ for any one preparation; C was independent of temperature and of the method of preparation, but k increased when excess of oxalate, and decreased when excess of silver ions, was used in the preparation. The activation energy (Fig. 3) was 27 kcal./mole for all preparations (Macdonald, *loc. cit.*, found 32 kcal./mole).

Pre-irradiation accelerated the subsequent thermal decomposition at 110°, according to the equation

$$C_i - C_u = \text{const.} \times I^2 t_i$$

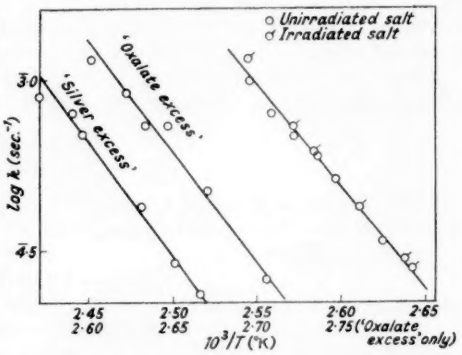
where t_i is the time of irradiation and C_i and C_u are the value of C [in equation (5)] for the irradiated and the unirradiated salt, respectively. Pre-irradiation, therefore, increases the

FIG. 2.



Thermal decomposition of silver oxalate, showing conformity with $p = C \exp(kt)$ for a few plots for unirradiated and irradiated salt at various temperatures.

FIG. 3.



Variation of the rate of thermal decomposition of silver oxalate with temperature for different preparations.

value of C, although equation (5) is still obeyed and the activation energy is unchanged (Fig. 3). Previously Tompkins found $C_i - C_u \propto I^{3{\cdot}3} t_i^{2{\cdot}8}$, but this result may be discounted since pre-irradiation was there performed in air when the silver nuclei react with oxygen and not *in vacuo* as in the present work.

All these results may be explained by a mechanism similar to that suggested by Macdonald (*loc. cit.*), but our additional data allow a more detailed and specific treatment. We assume that the activation energy for the formation of nuclei is high except at special surface lattice defects where it is low. These are later identified as slip lines. Consequently, nucleation at these special sites is rapid and, therefore, after the first few minutes, the reaction consists effectively of growth from a fixed number of reaction centres (N_0). The exponential law [equation (5)] is consistent with a branching mechanism, and there are good reasons (Macdonald, *loc. cit.*) for assuming branching of two-dimensional plate-like nuclei rather than linear branching chains. If the total number of all nuclei present at time t is N, and k_b is the branching coefficient, then the rate of formation of new nuclei is

$$dN/dt = k_b N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

so that

$$N = N_0 \exp(k_b t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Cubic particles being assumed, the size of a plate-like nucleus formed at $t = \tau$, after time t is

$$x = wk_g\,(t - \tau) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where k_g is the rate of growth of the nuclei into the interior of the crystal and w is their (constant) width, taken to be the linear dimension of the cubic particles. In other words, it is assumed that the N_0 surface nuclei consist of rows of decomposed oxalate ions extending the whole width of the particle, and that these penetrate into the crystal by the decomposition of successive rows beneath the first.

The total size of all nuclei at time t is

$$X = \int_{\tau=0}^{\tau=t} x\mathrm{d}N + N_0k_gt \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$= (N_0k_gw)/k_b)\{e^{k_bt} - 1\} . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Since $k \simeq 10^{-3}$ sec.$^{-1}$, for $t > 20$ min. (*i.e.*, $\alpha > 0{\cdot}04\%$ decomposition), equation (10) becomes

$$X = (N_0k_gw/k_b)\ \exp\ (k_bt)$$

The pressure of carbon dioxide developed is, therefore,

$$p = (FN_0k_gw/k_b)\ \exp\ (k_bt) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where F is a factor converting the number of radicals decomposed into our practical pressure units (mm. $\times$ 10^{-4}). In fact, the experimental results fit this equation over a slightly wider range than predicted, *i.e.*, from $t \simeq 10$—15 min., or $\alpha = 0{\cdot}03\%$, up to at least $\alpha = 30\%$, the limit to which the thermal decompositions were followed.

Since $$k_b = \beta\nu \exp\ (-E_b/\boldsymbol{R}T) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

and $$k_g = \nu \exp\ (-E_g/\boldsymbol{R}T) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where ν is the lattice frequency, E_b and E_g are the activation energies for branching and growth respectively, and β is a probability factor, equation (11) becomes

$$p = \frac{FN_0w\nu \exp\ (-E_g/\boldsymbol{R}T)}{\beta\nu \exp\ (-E_b/\boldsymbol{R}T)} \exp\ (k_bt) \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Macdonald (*loc. cit.*) has shown experimentally that $E_b \simeq E_g$, hence,

$$p = (FN_0w/\beta) \exp\ (k_bt) = C \exp\ (k_bt) \quad . \quad . \quad . \quad . \quad . \quad (15)$$

where $$C = FN_0w/\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

We note that (i) C is independent of temperature, as found experimentally; (ii) pre-irradiation increases the value of C by increasing the number of surface nuclei N_0, whereas β, being governed by crystallographic considerations in the interior of the crystal, is unaffected by radiation; (iii) the method of preparation affects k_b, but not E_b; this effect must, therefore, be confined to β, the probability factor. But since C is unaltered, it follows that N_0w and β must vary in such a way that their ratio remains constant. This criterion can be satisfied if nucleation and branching are both caused by the same type of lattice defect. Two such possibilities are illustrated in Fig. 4, where branching is considered to be facilitated either by a cation–anion vacancy pair or by a dislocation. Branching is then determined by the presence of a crystallographic imperfection and is not a consequence of the creation of an alternative reaction path requiring a lower activation energy. In view of the ease with which reaction could spread to a whole row simultaneously, the dislocation mechanism is to be preferred.

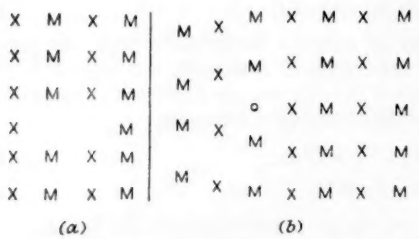
We have shown that, in prolonged photolysis, reaction proceeds at anion vacancies. If the same mechanism is retained for the thermal process, the activation energy for nucleation represents the energy required to transfer an electron from an oxalate ion into an anion vacancy. Since pre-irradiation certainly produces additional anion vacancies (N_v in number), the increase in the number of sites at which nucleation can occur (ΔN_0) should be related to N_v. For $I = 10^{15}$ quanta cm.$^{-2}$ sec.$^{-1}$, $N_v = 6 \times 10^{14}$ cm.$^{-2}$ at $t_i = 3{\cdot}2$ sec. The

area of salt exposed is approximately 0·3 cm.^{2}, and therefore $N_v = 2 \times 10^{14}$. From equation (16), we have

$$\Delta C/F = 2 \times 10^{14} Aw/\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

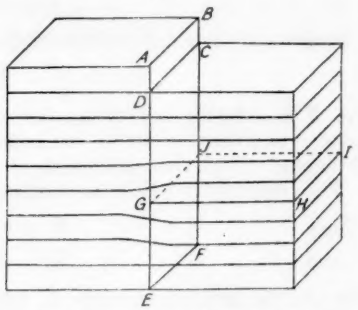
where A is a proportionality factor given by $\Delta N_0/N_v$. From the increase in C found experimentally, $\Delta C/F = 1{\cdot}8 \times 10^{13}$, so that $Aw/\beta = 0{\cdot}1$. From the experimental values of k_b and E_b, we find $\beta = 5 \times 10^{-2}$ for $\nu = 10^{13}$ sec.$^{-1}$; w is the number of ions per row in an average particle, and we consider that a value $w = 5 \times 10^3$ (corresponding to a cubic particle size of 10^{-4} cm.) is a reasonable estimate. This means that $A \simeq 10^{-6}$ and, therefore, that single anion vacancies are not highly effective in forming centres where nucleation can occur thermally. We interpret this as meaning that the activation energy for formation of nuclei is less at imperfections consisting of a group of anion vacancies than at single vacancies. Consequently, the reaction starts first at those places where pre-irradiation has decomposed a whole patch of oxalate ions. Now since nucleation and branching are both caused by the same (macro) imperfection and since the results of pre-irradiation indicate

FIG. 4.



Branching of reaction " chains " facilitated by (*a*) a cation–anion vacancy pair and (*b*) a dislocation. M = two Ag^+; X = oxalate ion; point o is referred to as an incipient vacancy.

FIG. 5.



Taylor–Orowan edge dislocation with slip line. Slip line *ABCD*; slip plane *AEFB*; additional " half-plane," *GHIJ*. Alternate planes parallel to *ABEF* contain silver or oxalate ions only. Fig. 4(*b*) represents a plane at right angles to the line *GJ*.

that single vacancies do not easily facilitate nucleation, we conclude that in the thermal decomposition of the unirradiated salt, nucleation starts at " steps " in the surface. For simplicity, we first consider a linear step provided by the slip line (*AD* in Fig. 5) of a Taylor–Orowan dislocation. Branching will occur when the decomposing row of anions meets the additional half-plane *GJHI*. Since branching occurs every time the advancing nucleus meets an extra half plane, the probability of branching will be given by

$$\beta = b/w \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

where b is the width of the slip line and w, as before, the total number of planes in the particle. Therefore

$$C/F = N_0 w/\beta = N_0 w^2/b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

Substituting the experimental values $C/F = 3{\cdot}2 \times 10^{12}$, $\beta = 0{\cdot}05$ as before, and our estimate of w, 5×10^3, we find $N_0 = 3 \times 10^7$; $b = 250$. Though no measurements on dislocations in silver oxalate are available, all the numerical values are of a reasonable order of magnitude, a dislocation density of 10^8 per cm.^{2} being quite normal even in a well-annealed crystal.

The real crystal, however, is more likely to contain general dislocation rings than simple Taylor–Orowan dislocations, but these also lead to slip lines in the surface (as indicated below) and, as far as surface nucleation is concerned, introduce no new features. However, the advantage gained is that the presence of dislocation rings leads naturally to an explan-

ation of the constant magnitude of C with various preparations, whereas we are unable to reach this conclusion using Taylor–Orowan dislocations unless a further assumption (for which we can find no justification) is made, *viz.*, that the width b of the slip line increases linearly with the number N_0 of slip lines in the surface.

Now the presence of excess of sodium oxalate during precipitation increases the probability of the incorporation of foreign cations. The presence of several of these at the edge of a growing plane is likely to cause cessation of growth resulting in a disc of vacancies (Seitz, *Phys. Review*, **1950, 79**, 239). When the opposite faces of the disc collapse, the general dislocation ring so formed will in general not lie in the principal slip plane and consequently act as a Frank–Read source (*ibid.*, *p.* 722) which generates slip lines in the surface of the crystal. Increased incorporation of foreign cations, therefore, increases the number of slip lines in the surface. These lines need only attain a thickness of several atomic layers since the stress set up by the Frank–Read source may be relieved by the anchoring effect of foreign ions (Koehler, " Imperfections in Nearly Perfect Crystals," Wiley and Sons Inc., New York, 1952, p. 200). Here b now represents the frequency of anchoring and is, therefore, proportional to the concentration of foreign ions, so that N_0/b, and therefore C, is independent of preparation as found experimentally.

Increase in silver nitrate in the mother-liquor reduces the probability of incorporation of foreign cations and hence the number of dislocations. Evidently the incorporation of foreign anions does not lead to sites where nucleation can occur.

Our picture of the freshly prepared salt is, therefore, that it consists of fine particles, each with the characteristic silver oxalate layer-lattice but containing a large number of ring dislocations with associated slip lines in the surface, and dislocation lines anchored in the interior of the crystal. Only prolonged pre-irradiation leading to large groups of surface anion vacancies is effective in increasing the normal thermal rate of decomposition. Many of these groups that facilitate nucleation will be situated above the randomly distributed closed dislocation rings which are operative in the branching process described above, and consequently such groups act as normal branching nuclei. The branching probability β is thus clearly a property of the crystal, and the only service rendered by pre-irradiation is to facilitate nucleus formation at sites where nuclei would not normally be formed in the unirradiated salt.

In a highly disorganized salt, where the branching coefficient is high (*i.e.*, β large), branching will predominate, leading to the exponential law

$$p = C \exp(k_b t)$$

This equation will be expected to hold only for a sample of silver oxalate in which the dislocation density is high. This will certainly be so for a salt freshly prepared by rapid precipitation, but with ageing, a process akin to annealing will occur at a slow rate, resulting in a decrease in both N_0 and β. If the number of rapidly formed nuclei at " steps " is small, those formed more slowly at single anion vacancies will be the controlling factor so that equation (6) must be reformulated as

$$\mathrm{d}N/\mathrm{d}t = k_f(N_0 - N)$$

or

$$N = N_0\{1 - \exp(-k_f t)\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

where k_f is the rate of formation of nuclei, N_0 being the number of potential centres. Previously, with N_0 large and branching rapid, the contribution of nuclei additionally created during decomposition was small, but with aged salt in which little branching can occur and normal growth predominates, this term cannot be neglected and, in the limit, controls the kinetics. For two-dimensional growth, we have, therefore,

$$p = \text{const.} \times \int_0^t k_g(t-\tau)^2 k_f N_0 \exp(-k_f\tau)\mathrm{d}\tau$$

or

$$p \simeq Dt^3, \text{ for } k_f \text{ small} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

Although with rapid branching the slow rate of growth perpendicular to the plate is negligible, yet in the well-aged salt this may not be so, in which case exponents between 3

and **4** may be expected in equation (21). Thus the power law found previously should be obtained when well-aged crystals are used, as when Tompkins, for example, used a preparation which had been preserved in the dark in a desiccator for over 6 months. To test this conclusion, Mr. D. A. Young, of this Department, has studied the thermal decomposition of the same sample of oxalate (I) which, when freshly prepared, had given an exponential p–t curve (measurements by A. F.) after ageing in the dark at room temperature for 6 months. The exponential law could be fitted only over the first 2—3% of decomposition, whereas a power law with exponents varying between 3·2 and 3·5 fitted the p–t plots over the range 3—35% of decomposition. It is thus possible, by using the present mechanism, to give a detailed picture of the decomposition of silver oxalate and to reconcile the views of various investigators.

One of us (A. F.) acknowledges the receipt of a scholarship granted by Education Department, South Shields, Co. Durham; we are indebted to Mr. D. A. Young for some experimental results and for valuable discussions.

IMPERIAL COLLEGE OF SCIENCE, S.W.7. [*Received, January 13th*, 1954.]

Purine Studies. Part I. Stability to Acid and Alkali. Solubility. Ionization. Comparison with Pteridines.

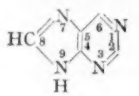
By ADRIEN ALBERT and D. J. BROWN.

[Reprint Order No. 4935.]

Syntheses of several new monosubstituted purines are described. In general, purines were found to be more stable than the corresponding pteridines: the electronic distribution responsible for this is discussed. Unexpectedly, 2-monosubstituted purines underwent a reversal of the Traube synthesis, giving 4 : 5-diaminopyrimidines.

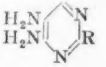
The cumulative effect of hydroxyl groups is to make purines progressively less soluble in water, but (contrary to E. Fischer's prediction) amino-groups *in excess of one* increase the solubility. The ionization constants of 34 purines are measured and discussed.

THIS study of the simpler purines follows the lines of a study of the simpler pteridines (Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 1620, 4219; Albert and Brown, *J.*, 1953, 74). The desirability of comparing purine (I) and pteridine (II) arises from the



(I)
(The hydrogen atom shown on $N_{(9)}$ is shared with $N_{(7)}$)

(II)



(III*a*; R = OH)
(III*b*; R = SMe)

similarity of their structure, and from the essential catalytic role played by pteridines in the natural synthesis of purines (Woolley and Pringle, *J. Amer. Chem. Soc.*, 1950, **72**, 634). Moreover, pteridines can be formed from purines by ring enlargement and may be formed thus in Nature (Albert, *Biochem. J.*, in the press).

Stability.—The results given in Table 1 were obtained by refluxing the purines with acid or alkali, as was done with the pteridines (Albert, Brown, and Cheeseman, *J.*, 1952, 4219). It is evident that purine, unlike pteridine, is highly stable: as with pteridine, hydroxyl groups stabilize it against attack by acid. But whereas pteridine is also stabilized by hydroxyl groups against attack by alkali, the reverse effect is found in the purine series when two or more hydroxyl groups are present, so that uric acid is distinctly unstable to alkali. The nature of this reaction is known to be oxidative (Brandenberger, *Helv. Chim. Acta*, 1954, **37**, 641).

The exceptional instability of 2-hydroxypurine to acids was further investigated. After only 5 minutes' boiling with N-sulphuric acid, appreciable quantities of 4-amino-5-formamido-2-hydroxypyrimidine and 4 : 5-diamino-2-hydroxypyrimidine (III*a*) were found. After two hours, no 2-hydroxypurine remained, and (III*a*) was isolated as the sparingly soluble quartasulphate in 25% yield (much of it had broken down further).

TABLE 1. *Decomposition (%) of purines.*

(A) From ammonia evolved, assumed to be mole per mole, (B) from spectrophotometric estimation of unchanged material (both 1 hr. at 100°).

	N-H_2SO_4		10N-NaOH	
Purine derivative	A	B	A	B
Unsubstituted	12	8 [b]	0	1
2-Hydroxy	12	92	2	2
6-Hydroxy (hypoxanthine)	1	2	1	1
8-Hydroxy	0	0	0	0
2 : 6-Dihydroxy (xanthine)	3	2	9·5	8
2 : 8-Dihydroxy	5	5	6	4
6 : 8-Dihydroxy	5	4	7	6
2 : 6 : 8-Trihydroxy (uric acid)	3	4	21	18
2-Mercapto	8	88	[c]	[c]
2-Amino [a]	10	4	1	1
$N_{(9)}$-Methyl	1	3	5	98

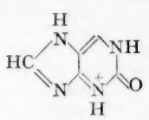
[a] Critical conditions for non-interference by 2 : 4 : 5-triaminopyrimidine were found at 267 mμ (pH 0). The yield of triaminopyrimidine in the acid hydrolysis was shown to be 5% by paper chromatography (solutions of known strength as controls). [b] Cf. pteridine (74%). [c] Not attempted.

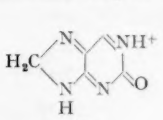
These reactions were also followed chromatographically on paper. By avoiding the usual excess of acid in its preparation (Johns, *J. Biol. Chem.*, 1912, **11**, 69; Tafel and Ach, *Ber.*, 1901, **34**, 1170), the yield of 2-hydroxypurine was improved.

Dilute acid readily attacked 2-mercaptopurine also (see Table 1), giving 4 : 5-diamino-2-mercaptopyrimidine. However, 2-aminopurine was not greatly affected under these conditions, although 2 : 4 : 5-triaminopyrimidine was found chromatographically in the product. No evidence of hydrolysis to (III*a*) could be found in either case. 2-Methylthiopurine was not attacked by acid.

Introduction of electron-releasing substituents into 2-hydroxypurine stabilizes it towards acids. For example, 2 : 6-dihydroxypurine (xanthine) resists 10N-hydrochloric acid at 100° (Fischer, *Ber.*, 1898, **31**, 2562), and uric acid withstands boiling 7N-hydrochloric acid or concentrated sulphuric acid at 100°. Other examples of this stabilization will be found in Table 1; also we found 2 : 6 : 8-triaminopurine was stable to N-sulphuric acid at 100°.

The instability to acids of 2-hydroxypurine must involve a cation, *e.g.*, (IV) or even (V), capable of stabilizing the pyrimidine ring at the expense of the glyoxaline ring.


(IV)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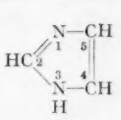
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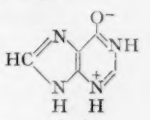
(VII)

Another example of a special instability caused by a 2-substituent is provided by the reaction of 2-methylthiopurine with aliphatic amines. 2-Methylthiopurine, when heated with mono- or di-methylamine at 155° for 24 hours, broke down to 4 : 5-diamino-2-methylthiopyrimidine (III*b*), whereas 6- and 8-methylthiopurine gave only the expected alkylaminopurines [for proof of the constitution of (III*b*) see p. 2067]. Neither methylamine nor 10N-sodium hydroxide affected 2-methylthiopurine at 100° (30 min.).

The instability to alkali of $N_{(9)}$-methylpurine (Table 1) is in line with Fischer's observation that hydroxypurines become highly sensitive to boiling N-potassium hydroxide when they are so substituted that they can no longer produce anions. For example, caffeine (1 : 3 : 7-trimethylxanthine) was completely destroyed in ¼ hour, whereas xanthine was barely

affected in 20 hours (*Ber.*, **1898**, **31**, 3266). 5-Amino-4-methylaminopyrimidine was isolated almost quantitatively after action of N-sodium hydroxide on 9-methylpurine (1 hour at 100°), and compared with authentic material (Brown, *J. Appl. Chem.*, **1954**, **4**, 72).

The reason for the increased stability of purine over pteridine is to be found in the different distribution of electrons in the two systems. Glyoxaline (VI) has a benzene-like

TABLE 2. *Physical properties of purines.*

No.	Purine derivative	Solubility in H_2O, 20° (±2°) 1 in	Solubility in H_2O, 100° 1 in	pK_a (in H_2O) and concn. (M) at which determined (20°)		R_F	Source
1	Unsubstituted	2	<1 [i]	—		0·80	A
	anion	—	—	8·93 (±0·02)	0·01	—	—
	cation	—	—	2·39 (±0·04) [j]	0·1	—	—
2	6-Methyl	5	—	—		0·85	B
	anion	—	—	9·02 (±0·02)	0·01	—	—
	cation	—	—	2·6	0·1	—	—
3	8-Methyl	18	6	—		0·85	A
	anion	—	—	9·37 (±0·05)	0·01	—	—
	cation	—	—	2·85 (±0·06)	0·1	—	—
4	$N_{(9)}$-Methyl	<2 [b]	—	—		0·85	A
	cation	—	—	2·36 (±0·03)	0·1	—	—
5	8-Phenyl	5,900	600	—		0·90	A
	anion	—	—	8·09 (±0·06)	0·001	—	—
	cation	—	—	2·68 (±0·07)	0·0017 [k]	—	—
6	6-Chloro	180	—	—		[r]	C
	anion	—	—	7·82 (±0·04)	0·01	—	—
	cation	—	—	<2	0·03	—	—
7	2-Hydroxy (+1H_2O)	380	22	—		0·40	A
	anion (mono)	—	—	8·43 (±0·03)	0·02	—	—
	anion (di)	—	—	11·90 (±0·07)	0·02	—	—
	cation	—	—	1·69 (±0·04)	0·02	—	—
8	6-Hydroxy (hypoxanthine)	1,400 [c]	70 [c]	—		0·55	F
	anion (mono)	—	—	8·94 (±0·02)	0·005	—	—
	anion (di)	—	—	12·10 (±0·03)	0·02	—	—
	cation	—	—	1·98 (±0·02)	0·025 [k]	—	—
9	8-Hydroxy	240	12	—		0·70	A
	anion (mono)	—	—	8·24 ±(0·03)	0·005	—	—
	anion (di)	—	—	>12	—	—	—
	cation	—	—	2·58 (±0·06)	0·005	—	—
10	2 : 6-Dihydroxy (xanthine)	2,000 [da]	400 [e]	—		[s]	D
	anion (mono)	—	—	7·44 (±0·04) [l]	0·001	—	—
	anion (di)	—	—	11·12 (±0·04)	0·001	—	—
11	2 : 8-Dihydroxy	26,000 [f]	2500	—		0·30	E
	anion [g]	—	—	7·45 (±0·10) [f]	—	—	—
12	6 : 8-Dihydroxy	6,000	350	—		0·40	A
	anion (mono)	—	—	7·65 (±0·07)	0·002 [k]	—	—
	anion (di)	—	—	9·87 (±0·07)	0·002 [k]	—	—
13	2 : 6 : 8-Trihydroxy (uric acid)	39,500 [g]	1262 [g]	5·4 [m]	—	0·30	—
14	2-Methoxy	200	—	—		0·90	A
	anion	—	—	9·2	0·01	—	—
	cation	—	—	2·44 (±0·08)	0·001	—	—
15	6-Methoxy (+0·5H_2O)	225	—	—		0·85	B
	anion	—	—	9·16 (±0·05)	0·005	—	—
	cation	—	—	2·21 (±0·02)	0·02	—	—
16	2-Amino	120	3·5	—		0·55	A
	anion	—	—	9·93 (±0·03)	0·05	—	—
	cation (mono)	—	—	3·80 (±0·01)	0·05	—	—
	cation (di)	—	—	−0·28 [f]	—	—	—
17	6-Amino (adenine)	1,100 [h]	40 [h]	—		0·70	D
	anion	—	—	9·8 [n]	—	—	—
	cation (mono)	—	—	4·22 (±0·02)	0·005	—	—
	cation (di)	—	—	<1	0·05 [k]	—	—
18	8-Amino	2,000	600	—		0·50	A
	anion	—	—	9·36 (±0·08)	0·003	—	—
	cation	—	—	4·68 (±0·02)	0·01 [k]	—	—
19	2 : 6-Diamino	420	17	—		0·55	D
	anion	—	—	10·77 (±0·05)	0·02	—	—
	cation (mono)	—	—	5·09 (±0·05)	0·02	—	—
	cation (di)	—	—	<1	—	—	—

TABLE 2. (*Continued.*)

No.	Purine derivative	Solubility in H_2O, 20° (±2°) 1 in	Solubility in H_2O, 100° 1 in	pK_a (in H_2O) and concn. (M) at which determined (20°)		R_F	Source
20	2 : 6 : 8-Triamino	200	20	—		0·40	B, H
	anion	—	—	10·79 (±0·04)	0·033	—	—
	cation (mono)	—	—	6·23 (±0·07)	0·033	—	—
	cation (di)	—	—	2·41 (±0·05)	0·033	—	—
21	6-Methylamino	850	50	—		0·80	A, F
	anion	—	—	9·99 (±0·05)	0·007	—	—
	cation (mono)	—	—	4·18 (±0·02)	0·007	—	—
	cation (di)	—	—	<1	—	—	—
22	8-Methylamino	450	60	—		0·60	A
	anion	—	—	9·56 (±0·04)	0·01	—	—
	cation	—	—	4·78 (±0·04)	0·01	—	—
23	2-Dimethylamino	3,000	—	—		0·99	A, B
	anion	—	—	10·22 (±0·10)	0·002	—	—
	cation	—	—	4·02 (±0·03)	0·002	—	—
24	6-Dimethylamino	120	15	—		0·85	A
	anion	—	—	10·5 [p]	0·02	—	—
	cation (mono)	—	—	3·87 (±0·04)	0·02	—	—
	cation (di)	—	—	<1	—	—	—
25	8-Dimethylamino	150	3	—		0·65	A
	anion	—	—	9·73 (±0·03)	0·02	—	—
	cation (mono)	—	—	4·80 (±0·03)	0·03	—	—
	cation (di)	—	—	<1	—	—	—
26	2-Amino-6-hydroxy (guanine)	200,000	—	—		[e]	D
	anion (mono)	—	—	9·2 [n]	—	—	—
	anion (di)	—	—	12·3 [n]	—	—	—
	cation	—	—	3·3 [n]	—	—	—
27	6-Amino-2-hydroxy (*iso*guanine)	16,000	4000	—		0·40	A
	anion	—	—	8·99 (±0·2)	—	—	—
	cation	—	—	4·51 (±0·2) [f]	—	—	—
28	2-Mercapto	2,500	300	—		0·35	A
	anion (mono)	—	—	7·15 (±0·05)	0·0025	—	—
	anion (di)	—	—	10·4 [p]	0·0025	—	—
	cation	—	—	0·5 (±0·3) [f]	—	—	—
29	6-Mercapto	4,000	180	—		0·60	F
	anion (mono)	—	—	7·77 (±0·02)	0·0015	—	—
	anion (di)	—	—	10·84 (±0·04)	0·0015	—	—
	cation	—	—	<2·5 [q]	—	—	—
30	8-Mercapto	2,200	60	—		0·80	A
	anion (mono)	—	—	6·64 (±0·02)	0·0025	—	—
	anion (di)	—	—	11·16 (±0·09)	0·0025	—	—
	cation	—	—	<2·5 [q]	—	—	—
31	2-Methylthio	2,200	150	—		0·90	A
	anion	—	—	8·91 (±0·03)	0·0025	—	—
	cation	—	—	1·91 (±0·07)	0·0025	—	—
32	6-Methylthio	1,300	20	—		0·90	F
	anion	—	—	8·74 (±0·01)	0·005	—	—
	cation	—	—	0 (±0·2) [f]	—	—	—
33	8-Methylthio	650	65	—		0·90	A
	anion	—	—	7·67 (±0·01)	0·01	—	—
	cation	—	—	2·95 (±0·05)	0·01	—	—
34	2-Amino-8-phenyl	—	—	—		—	G
	anion	—	—	9·20 (±0·02)	0·001	—	—
	cation	—	—	3·98 (±0·07)	0·001	—	—

[a] No evidence of other species could be found spectrometrically. [b] 1 g. is dissolved by 1·7 ml. Fischer, *Ber.*, 1897, **30**, 2227. [d] At 10°. [e] Strecker, *Annalen*, 1861, **118**, 151 (*q.v.* for discussion of earlier figures). [f] Determined spectrometrically. [g] His and Paul, *Z. physiol. Chem.*, 1901, **31**, 29; Rossi, *Biochem. Z.*, 1913, **54**, 299. [h] Kossel, *Z. physiol. Chem.*, 1886, **10**, 254; Tafel and Ach, *Ber.*, 1901, **34**, 1175. [i] 1 g. is dissolved by 0·9 ml. [j] Equiv. to 2·30 at 0·001M. [k] Back-titrated. [l] Cf. 7·7 (Ogston, *J.*, 1935, 1376; hydrogen electrode). [m] Bernouilli and Loebenstein, *Helv. Chim. Acta*, 1940, **23**, 245. [n] Taylor, *J.*, 1948, 765. [p] Decomposed by alkali. [q] Spectrophotometry revealed no inflections down to pH 0. [r] Travels with front. [s] Is not visible in this solvent, but 3% ammonium chloride was suitable.

Sources: A, This paper. B, Kindly presented by Dr. Gertrude Elion (unpublished work). C, Kindly presented by Dr. Aaron Bendich (unpublished work). D, Commercial preparation, purified until a single spot was obtained (paper chromatography), and the potentiometric titration curve became regular. E, Johns, *Amer. Chem. J.*, 1911, **45**, 84. F, Elion, Burgi, and Hitchings, *J. Amer. Chem. Soc.*, 1952, **74**, 411. G, Falco, Elion, Burgi, and Hitchings, *ibid.*, p. 4897. H, Cavalieri and Bendich, *ibid.*, 1950, **72**, 2587.

inertness. It is stable to boiling 60% hydriodic acid, to chromic–sulphuric acid, and to distillation over lime (Ackermann, *Z. physiol. Chem.*, 1910, **65**, 508). It forms 4-nitroglyoxaline with nitric acid at 100° (Fargher and Pyman, *J.*, 1919, **115**, 219). This aromatic behaviour is derived from a sextet of unlocalized π-electrons, two being supplied from each double bond and the remaining two from the NH group. Delocalization is so effective as to leave that nitrogen atom with a formal positive charge. In acid and alkaline solution, glyoxaline is stablilized by further resonance, the anion and the cation being symmetrical structures. Benziminazole, in which a glyoxaline and a benzene nucleus are combined, is also stable, *e.g.*, it is unchanged by 10N-hydrochloric acid at 270° (O. Fischer, *Ber.*, 1889, **22**, 644). In pyrimidine both nitrogen atoms are doubly bound (of the type –N=) and hence have a formal negative charge. Each of these atoms competes for the six π-electrons, but the C : N= ratio of 4 : 2 does not endanger stability under mild conditions (however, pyrimidine is more sensitive to alkali than pyridine; Lythgoe and Rayner, *J.*, 1951, 2323).

Pteridine (II), which consists of two 6-membered rings, has 10 ring-atoms contributing 10 π-electrons which tend to accumulate on the four negatively charged nitrogen atoms (note the highly unfavourable C : N= ratio of 6 : 4). The outstanding instability of pteridine to acid and alkali (and its stabilization by electron-releasing substituents) has been traced to this electronic distribution (Albert, Brown, and Cheeseman, *J.*, 1952, 4219). In purine, on the contrary, the excess of π-electrons provided by the glyoxaline ring (5 ring-atoms : 6 π-electrons) plus the presence of a positively charged nitrogen atom in this ring, create a molecule in which the π-electron density is nowhere very low. That there is sharing of π-electrons between the glyoxaline and the pyrimidine ring follows from the ionization constants (see below). It is relevant that, whereas glyoxaline couples with diazotized aniline (in the 2-position; Fargher and Pyman, *loc. cit.*), we find that purine does not couple. However, it does couple if an electron-releasing substituent is introduced into the 2- or the 6-position: Fischer (*Z. physiol. Chem.*, 1909, **60**, 69) showed that this coupling took place in the 8-position. Pteridines, on the other hand, do not couple even when three electron-releasing groups are present (Albert, Brown, and Cheeseman, *J.*, 1952, 1620). Possible evidence for a slight localization of π-electrons in the glyoxaline ring is furnished by the ease with which the hitherto unknown 8-aminopurine diazotizes and couples (red) with β-naphthol, like the similarly constituted 2-aminoglyoxaline (Fargher and Pyman, *loc. cit.*). 2-Amino-, 6-amino-, and 2 : 6-diamino-purine do not couple.

Solubility in Water.—The solubility of a number of purines has been determined and is shown in Table 2. The following remarks apply especially to solubility at 20°. Purine (I), unlike pteridine (II), has a hydrogen available for hydrogen-bond formation, and presumably exists in the solid phase as a chain of molecules, hydrogen-bonded between the 7- and the 9-positions of neighbours. This would account for the high m. p. (213°) compared with that of pteridine (140°). Evidently this type of hydrogen-bond does not compete favourably with hydrogen bonding to water molecules, because purine is very soluble in water, even more so than pteridine which cannot form hydrogen bonds. Understandably, the solubility is lowered by lipoid-solubilizing groups (*e.g.*, Me, Cl, MeS, Ph; Nos. 2, 3, 6, 31, 32, 33, and 35), the larger groups having the greater effect. On the other hand, a 9-methyl group (No. 4) slightly increases the solubility by preventing hydrogen-bonding (m. p. 161° and, unlike purine, lipoid-soluble).

The monohydroxypurines (Nos. 7—9) resemble the hydroxypteridines in being one hundred (or more) times less soluble in water than the parent substance. This decrease is attributed to unusually strong crystal-lattice forces originating in hydrogen bonding between the hydroxy-groups and the ring-nitrogen atoms (Albert, Brown, and Cheeseman, *J.*, 1952, 4219). This increased strength, it is now suggested, comes from the reinforcement afforded by strong dipoles, of the type (VII). In harmony with this concept, methoxypurines are more soluble than the corresponding hydroxypurines (see Nos. 14 and 15; 8-methoxypurine is still unknown).

The dihydroxypurines (Nos. 10—12) are less soluble than the monohydroxypurines; trihydroxypurine (No. 13) is the least soluble of all. Various figures for xanthine (No. 10) are available in the literature, and we have used Strecker's because he has given the subject

critical attention. 2 : 8-Dihydroxypurine resembles xanthine in being apparently amorphous and tending to give supersaturated solutions, but the other substances in Table 2 reached equilibrium rapidly and deposited well-defined crystals.

The monoaminopurines (Nos. 16—18) are all less soluble than purine. The order of insolubility ($2 < 6 < 8$) for the monoaminopurines also holds if the 7- or the 9-hydrogen atom is replaced by methyl (Fischer, *Ber.*, 1899, **32**, 435). Fischer (*ibid.*, p. 498) suggested that the polyamino-purines would be less soluble still, in analogy with the hydroxypurines. This is not so, as Nos. 19 and 20 show (cf. 13 and 20, for instance). It is evident that, in this series at least, amino-groups in excess of one can be more attracted to water than to other molecules of the purine. As would be expected from our hypothesis of hydrogen bonding, the monomethylaminopurines are more soluble than the aminopurines, and the dimethylaminopurines more soluble still (Nos. 21—25). However, 2-dimethylaminopurine forms an exception: it is surprisingly insoluble although normal in other respects (*e.g.*, in the relation of the spectra, and of the pK's, to those of the parent compound).

As with pteridines, the aminohydroxypurines (Nos. 26 and 27) are far less soluble than the corresponding dihydroxy- or diamino-purines. This is attribtued to the dipole's being much more powerful in such substances. Similarly, 6-amino-2 : 8-dihydroxypurine is soluble only 1 in 500,000 at 23° (Bendich, *J. Biol. Chem.*, 1950, **183**, 267).

The mercaptopurines (Nos. 28—30) are less soluble than the corresponding hydroxypurines (Nos. 7—9). Because neither hydrogen bonding nor dipole moments should be as great as in the hydroxy-analogues, the principal consideration must be the lower hydrophilic properties of sulphur in comparison with oxygen. Hence it is not surprising that *S*-methylation (Nos. 31—33) improves solubility less effectively than does *O*-methylation.

Ionization.—A number of ionization constants have been determined (see Table 2). The ionization of purine, not previously investigated, yields an anion of pK_a 8·9 (*i.e.*, a little stronger than phenol) and a cation of pK_a 2·4 (*i.e.*, considerably weaker than aniline or pyridine). The values for glyoxaline (VI) [13 and 7·0 respectively (Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146; Wieland and Schneider, *Annalen*, 1953, **580**, 159)] are changed, on the addition of a benzene ring (giving benziminazole), to 12·3 and 5·5 respectively, *i.e.*, the acid strength has become stronger and the base strength weaker (Albert, Goldacre, and Phillips, *J.*, 1948, 2240). The base strength of pyrimidine is very weak (1·3; Albert, Goldacre, and Phillips, *loc. cit.*) and, as it is a more electron-attracting nucleus than benzene, the above values for purine may seem a natural consequence of combining the glyoxaline and the pyrimidine nucleus. It cannot be disputed that the anion is formed by the loss of a proton from the glyoxaline ring, but it does not follow that the cation is formed by the capture of a proton in the glyoxaline ring. The cationic pK_a (2·4) is just as compatible with a pyrimidine nucleus enriched by the electrons which the glyoxaline nucleus is surrendering. This poses a problem which diffraction crystallography could solve.

Methyl substituents show their usual (but feeble) acid-weakening and base-strengthening properties (Nos. 2 and 3). 9-Methylpurine has no acidic properties because methyl has replaced the ionizable hydrogen. The 8-phenylpurines (Nos. 5 and 34) show the expected acid-strengthening. Chlorine (in No. 6) proves to be acid-strengthening and base-weakening, as expected.

The introduction of a hydroxyl group into purine (Nos. 7—9) permits the formation of two anions. It is not easy to determine, in each case, whether the imino- or the hydroxy-group is the stronger. For example, the anionic pK's of purine, 6-hydroxypurine, and 6-hydroxy-9-methylpurine are the same (8·9). Fortunately the hydroxyl group in 6-hydroxypurine is so placed with regard to $N_{(7)}$ as to form chelate complexes: it was found that a steady stability constant can be obtained from the titration curves (in the presence of various metallic cations) only if it is assumed that the group which chelates has the lower anionic pK_a (Albert, *Biochem. J.*, 1953, **54**, 646). This implies that the value 8·9 belongs to the hydroxyl group of 6-hydroxypurine. This form of reasoning does not help with the isomers, which do not form chelate complexes.

Attention is drawn to the cationic constant of 6-hydroxypurine, hitherto overlooked, apparently because it does not influence the spectrum [pK's of 10·3 and 0·6 obtained for

this substance by a solubility method (Filitti, *J. Chim. phys.*, 1935, **32**, 1) are evidently incorrect]. Further hydroxyl groups progressively increase acidic strength (Nos. 10—13). They also weaken basic strength: solubility difficulties prevent exact measurement, but Wood's figure of pK_a 0·8 for xanthine may be a guide (*J.*, 1906, **89**, 1840).

As expected, an amino-substituent (Nos. 16—26) is acid-weakening. The rather large consequent increase in basic strength indicates that the principal basic centre has shifted to a guanidino-group which includes the amino-substituent. It is relevant that *X*-ray crystallography of adenine (No. 17) hydrochloride has revealed that the proton is on $N_{(1)}$ (Cochran, *Acta Cryst.*, 1951, **4**, 81). As would be expected, further substitution by amino-groups increases the base-strengthening effect, and triaminopurine (No. 20) has pK_a 6·2, the most basic of known purines. The mono- and di-methylation of the amino-purines progressively decreases acid strength without greatly changing base strength (Nos. 21—25).

As would be expected, the mercaptopurines (Nos. 28—30) are more acidic than the hydroxy-analogues (Nos. 7—9). The effect of a methylthio-group in a benzene nucleus is slightly to weaken bases and either to strengthen acids or not affect them (Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058). These effects are observed also in Nos. 31—33, but the base-strengthening in No. 33 was unexpected.

In comparisons of the ionization of purine and pteridine, the most important differences are that the latter is a stronger base (pK_a 4·1) and has no imino-group with which to form an anion. No equivalent has been found in the purine series to (*a*) the hysteresis encountered in titrating 6-hydroxypteridine (Albert, Brown, and Cheeseman, *J.*, 1952, 1620), (*b*) the curious base-weakening properties of methylpteridines (to be reported later), or (*c*) the mutual weakening of amino- and hydroxy-groups in aminohydroxypteridines (Albert, Brown, and Cheeseman, *J.*, 1952, 4219).

Syntheses.—Purine is usually prepared from uric acid, in 2% yield, by Fischer's method (*Ber.*, 1898, **31**, 2550). The recent accessibility of 4 : 5-diaminopyrimidine (Brown, *J. Appl. Chem.*, 1952, **2**, 239) prompted us to re-examine Isay's method (*Ber.*, 1906, **39**, 250), in which this amine is heated with formic acid to 210° and the product distilled. The usual poor yields were found to be caused by destruction during the distillation: the purine was present in the reaction mixture as a formate from which it was liberated by calcium carbonate refluxing in alcohol (85% yield). Attempts to methylate purine were unsuccessful, including (*a*) use of methyl sulphate at pH 8·5, (*b*) heating with methyl iodide alone, or in aqueous sodium hydroxide, (*c*) use of methyl toluene-*p*-sulphonate at 150°, (*d*) heating with formic acid and formaldehyde, and (*e*) heating the mercurichloride with methyl iodide. It also resisted hydroxymethylation with formaldehyde.

9-Methylpurine was obtained in excellent yield by refluxing 5-amino-4-methylaminopyrimidine (Brown, *J. Appl. Chem.*, 1954, **4**, 72) with formic acid. In the usual method a trivial yield is obtained, by a lengthy series of reactions, from uric acid (Fischer, *loc. cit.*).

2-Dimethylaminopurine was prepared by formylating 4 : 5-diamino-2-dimethylaminopyrimidine in the 5-position and heating the product at 260°. A specimen prepared from these intermediates under other conditions (Miss G. Elion, unpublished work) was used to confirm the unexpectedly low solubility (Table 2). A similar attempt to prepare 2-methoxypurine gave only a 10% yield because diformylation largely supervened: the second product was not basic and was thus probably 4 : 5-diformamido-2-methoxypyrimidine. 4-Amino-2-methoxy-5-nitropyrimidine resisted formylation even by acetic formic anhydride. Isay's synthesis of 2-aminopurine (*loc. cit.*, *Ber.*) has been improved.

2-Mercaptopurine was obtained by refluxing 4 : 5-diamino-2-mercaptopyrimidine with formic acid. When this work was complete, a synthesis of this substance under more vigorous conditions, and in lower yield, was described by Robins, Dille, Willits, and Christensen (*J. Amer. Chem. Soc.*, 1953, **75**, 263). With chloroacetic acid, it gave 2-carboxymethylthiopurine, but this could not be hydrolysed to 2-hydroxypurine even on 3 hours' refluxing with 48% hydrobromic acid. 2-Mercaptopurine was converted into 2-methylthiopurine with methyl iodide. The position of the methyl group was confirmed by direct synthesis: 4-amino-2-chloro-5-nitropyrimidine with sodium methyl sulphide gave 4-amino-2-methylthio-5-nitropyrimidine; this was hydrogenated to the 4 : 5-diamine (III*b*), which was condensed with formic acid to give the 5-formamido-derivative.

This was cyclized to 2-methylthiopurine at 185°. 4 : 5-Diamino-2-methylthiopyrimidine was also prepared by the methylation of 4 : 5-diamino-2-mercaptopyrimidine.

Some improved syntheses of 6-substituted purines are given in the Experimental section.

Among several new 8-substituted purines, 8-phenylpurine was prepared by benzoylating 4 : 5-diaminopyrimidine, separating the di- and the mono-benzoyl derivative, and heating the latter at 230°. 8-Methylthiopurine was made by methylating 8-mercaptopurine. It evolved methanethiol copiously when boiled with N-hydrochloric acid, thus confirming the attachment of the methyl group to S. When heated with ammonia, methylamine, and dimethylamine it gave respectively 8-amino-, 8-methylamino-, and 8-dimethylamino-purine. 6 : 8-Dihydroxypurine was synthesized in a new and more convenient way from urea and 4 : 5-diamino-6-hydroxypyrimidine. Improvements have been affected in the preparation of 8-methyl-, 8-hydroxy-, and 8-mercapto-purine. The last-named was converted into 8-carboxymethylthiopurine which gave only a poor yield of 8-aminopurine when heated with ammonia. A trace of 8-aminopurine was obtained by the action of cyanogen bromide on 4 : 5-diaminopyrimidine, a reaction that is more successful in the benziminazole series (Pierron, *Ann. Chim.*, 1908, **15**, 193).

Experimental

Yields of substances that lack a m. p. refer to the stage where they appeared homogeneous in paper chromatography in 3% aqueous ammonium chloride or butanol–5N-acetic acid. Microanalyses were by Mr. P. R. W. Baker, Beckenham. R_F values (as in Table 2) were obtained in butanol–5N-acetic acid (2 : 1) by the descending method, picric acid (R_F 0·80) being used as a control.

Solubilities.—Those recorded in Table 2 were determined as described by Albert, Brown, and Cheeseman, *J.*, 1952, 4219.

Ionization Constants.—Except where otherwise noted in Table 2, these were determined potentiometrically, as described by Albert, Brown, and Cheeseman (*J.*, 1951, 474). The pK's of pyrimidines required for the spectrometric analyses reported in Table 1 were taken from Part II.

Decomposition by Alkali.—Each purine (0·001 mole) was heated under reflux with 10N-sodium hydroxide (10 ml.) at 110° (bath) for 1 hr., then steam-distilled in a Kjeldahl apparatus for 20 min., at constant volume. The evolved ammonia was trapped in 0·1N-hydrochloric acid (25 ml.), and determined by back-titration. The contents of the distillation-flask were then diluted (after neutralization, where necessary) with an appropriate buffer solution to 10^{-4}M. The densities, at wave-lengths known to be significant for the starting material, in its various ionic species, were then compared in an ultra-violet spectrophotometer, of which the solvent cell contained an aqueous solution of the same amount of the same salts brought to the same pH.

Each spectrometrically determined decomposition figure in Table 1 was calculated from that peak showing the greatest loss in density (compared with the corresponding peak in the corresponding species of untreated substance). This examination of a number of peaks, and species, was designed to minimize error due to the possibility of the decomposition products' having some peaks at wave-lengths near to those of the starting material.

Decomposition by Acid.—The purines (0·001 mole) were heated as above, but with N-sulphuric acid (10 ml.). The resulting solution (or suspension) was diluted to 50 ml., of which 25 ml. were transferred to a Kjeldahl apparatus. 10N-Sodium hydroxide (3 ml.) was added and the contents were steam-distilled (at constant volume) for 20 min., the evolved ammonia being determined as above. Corrections were made, where necessary, for any ammonia evolved through alkaline decomposition during this distillation.

Purine.—4 : 5-Diaminopyrimidine (4·4 g., 0·04 mole; Brown, *J. Appl. Chem.*, 1952, **2**, 239) and formic acid (20 ml.) were heated at 100° under carbon dioxide for 15 min., then at 210° during 45 min. and at 210° for 30 min. The product was rapidly cooled, powdered finely, and heated to constant weight at 110—120°. The dark powder was refluxed for 3 hr. in alcohol (100 ml.) with calcium carbonate (2 g.). The suspension was filtered and the residue was dried, finely ground, and refluxed for 30 min. with alcohol (40 ml.). The combined filtrates, taken to dryness gave 4·1 g. of purine (85%), m. p. 212—213°. Sublimation at 175°/0·01 mm. gave faintly yellow crystals (93% recovery), m. p. 212—213°; recrystallization, by dissolution in boiling

alcohol (1 g. in 13 ml.) and concentration to one-third volume, removed the yellow colour (90% recovery), m. p. 212—213° (cf. 211—212° given by Fischer, *Ber.*, 1898, **31**, 2550).

9-*Methylpurine*.—5-Amino-4-methylaminopyrimidine (2 g.) was refluxed with formic acid (98%; 4 ml.) for 2 hr. The acid was removed at 100°/20 mm. Alcohol (4 ml.) was added to the oily residue and the mixture evaporated. Sublimation at 140—150°/20 mm. gave white crystals (1·7 g.) of 9-methylpurine. After recrystallisation from *iso*butyl methyl ketone (7 parts), it had m. p. 159—161° [Fischer gives 162—163° (corr.)] (Found: N, 41·5. Calc. for $C_6H_6N_4$: 41·8%). The compound discolours slowly in sunlight.

2-*Hydroxypurine*.—A solution of 2-aminopurine (2·7 g.; 0·02 mole) in acetic acid (10 ml.) and water (10 ml.) was super-cooled to 20°. Sodium nitrite (1·4 g.) in water (6 ml.) was added dropwise during 5 min. at < 30°. Next day, the gelatinous precipitate was filtered off, recrystallized from water (20 parts) and dried at 110°, giving 2-hydroxypurine as creamy-white crystals (65%), homogeneous on paper chromatography with aqueous ammonium chloride (3%) (Found: C, 39·0; H, 3·9; N, 36·4. Calc. for $C_5H_4ON_4,1H_2O$: C, 39·0; H, 3·9; N, 36·35%). When boiled with 2 equivs. of N-sulphuric acid for 2 hr. and adjusted to pH 4·5, 2-hydroxypurine gave a precipitate of 4 : 5-diamino-2-hydroxypyrimidine quartasulphate, which was recrystallised from 100 parts of boiling water (25% yield) (Found: C, 32·0; H, 4·2; N, 37·3. Calc. for $C_4H_6ON_4,\frac{1}{4}H_2SO_4$: C, 31·9; H, 4·35; N, 37·2%).

2-*Aminopurine*.—2 : 4 : 5-Triaminopyrimidine (7·5 g.; Albert, Brown, and Cheeseman, *J.*, 1951, 474), formylmorpholine (15 ml.; Médard, *Bull. Soc. chim.*, 1936, **3**, 1343), and formic acid (3 ml., 1·2 equivs.) were heated under reflux at 200° for 1 hr. Acetone (50 ml.) precipitated the 2-aminopurine which was dissolved in boiling water (25 ml.). The solution was passed through a wide filter, cooled to 50°, and diluted with 3N-nitric acid (12 ml.). After refrigeration, the nitrate was filtered off, suspended in boiling water (15 ml.), and brought to pH 6—8 with N-sodium citrate (1 ml.) and 6N-sodium hydroxide. The solution was boiled with carbon, filtered, and refrigerated, giving buff-coloured crystals of 2-aminopurine (50%). This was recrystallised from 4 parts of boiling water (carbon) until colourless, and became anhydrous when dried at 110°.

2-*Dimethylaminopurine*.—Crude 4 : 5-diamino-2-dimethylaminopyrimidine (3 g.; Albert *et al.*, *loc. cit.*) was refluxed with 98% formic acid (10 ml.) for 20 min., evaporated at 100° *in vacuo*, treated with water (40 ml.), warmed to 60°, and brought by ammonia to pH 7. The black precipitate was collected after refrigeration and crystallized (carbon) from water (140 ml.) (yield, 1·2 g.). Recrystallization from water (90 parts; carbon) gave white needles of 4-*amino*-2-*dimethylamino*-5-*formamidopyrimidine*, m. p. 235° (Found: C, 46·15; H, 6·1; N, 38·9. $C_7H_{11}ON_5$ requires C, 46·4; H, 6·1; N, 38·65%). This (0·9 g.) was plunged into a bath at 255—260° until evolution of water was complete (about 3 min.). The residue (0·72 g.) was recrystallized twice from water (45 parts; carbon) to give white 2-dimethylaminopurine, m. p. 222—223° (Found: C, 51·55, H, 5·6; N, 43·0. Calc. for $C_7H_9N_5$: C, 51·5; H, 5·6; N, 42·9%).

2-*Methoxypurine*.—Crude, dried 4 : 5-diamino-2-methoxypyrimidine (1 g.; Albert *et al.*, *J.*, 1952, 4219) and acetic formic anhydride (5 ml.) were heated at 50° for 1 hr. The solution was evaporated *in vacuo*, giving a solid (A). Alcohol (5 ml.) was added and the mixture evaporated. The residue was sublimed at 160°/0·1 mm. for 2 hr. The sublimate was recrystallized *at once* from alcohol (6 ml.), to give white nodules of 2-*methoxypurine*, m. p. 205—206° (10%) (Found: C, 48·0; H, 4·15; N, 37·1. $C_6H_6ON_4$ requires C, 48·0; H, 4·05; N, 37·3%). It is soluble in 25 parts of boiling alcohol. The preparation could not be scaled up without loss. Formic acid could not be substituted for the anhydride. When the solid A (above) was stirred with hot water (5 ml.), a solid (0·5 g.) separated. This was recrystallised from alcohol (75 parts), giving white needles of 4 : 5-*diformamido*-2-*methoxypyrimidine*, m. p. 180—181° (decomp.) (Found: C, 42·9; H, 4·1; N, 28·5. $C_7H_8O_3N_4$ requires C, 42·85; H, 4·1; N, 28·55%).

2-*Mercaptopurine*.—Formic acid (98%; 100 ml.) and 4 : 5-diamino-2-mercaptopyrimidine (20 g.) were refluxed vigorously for 3 hr. The suspension was kept at 0° for 12 hr. and the solid filtered off. A second crop was obtained by concentration. It was dissolved in 0·25N-sodium hydroxide (700 ml.), and reprecipitated with acetic acid (pH 4) (yield, 16 g., 73%). It was twice recrystallized from water (130 parts) to give yellow needles of 2-mercaptopurine which, dried at 110°, retained 0·25 mol. of water, which was lost at 150° [Found: C, 38·3; H, 3·05; N, 35·7; S, 20·3. Calc. for $(C_5H_4N_4S)_4,H_2O$: C, 38·3; H, 2·9; N, 35·75; S, 20·45%]. It decomposed slowly about 250°.

2-*Carboxymethylthiopurine*.—2-Mercaptopurine quartahydrate (2·4 g.) and chloroacetic acid (1·5 g.) in water (100 ml.) were refluxed for 2½ hr. After refrigeration the solid (2·8 g.) was filtered off and washed with water (5 ml.). Recrystallization from water (65 parts; carbon)

gave 80% recovery of white plates of 2-*carboxymethylthiopurine* (anhyd. after being dried at 130°), decomp. *ca.* 200° (Found: N, 26·7. $C_7H_6O_2N_4S$ requires N, 26·7%).

2-*Methylthiopurine*.—Methyl iodide (2·6 ml.) was added to a solution of 2-mercaptopurine hydrate (6·5 g.) in 5% aqueous sodium hydroxide (40 ml.), with shaking, during 20 min. After 2 hr. the whole was brought to *ca.* pH 5. It was refrigerated and the solid was filtered off and recrystallized from boiling water (700 ml.), to give 2-*methylthiopurine* as white needles (4·35 g., 64%), m. p. 250—255° (decomp.) (Found: C, 43·4; H, 3·55; N, 33·7; S, 18·9. $C_6H_6N_4S$ requires C, 43·35; H, 3·65; N, 33·7; S, 19·3%). It was readily soluble in hot alcohol (see below for an alternative synthesis).

4-*Amino*-2-*methylthio*-5-*nitropyrimidine*.—Methanethiol [freshly generated from *S*-methylthiourea sulphate (25 g.) and 5N-sodium hydroxide (40 ml.)] was passed into ethanolic N-sodium hydroxide (75 ml.). The solution was added during 5 min. to 4-amino-2-chloro-5-nitropyrimidine (8·75 g.) in hot ethanol (875 ml.). After 10 min., carbon dioxide was passed through the solution until it reached room temperature. The mixture was chilled and filtered. The solid was ground under water and refiltered. The yellow residue (8·0 g.; m. p. 180°) was recrystallized twice from alcohol (50 parts), giving colourless plates (5·3 g.) of 4-*amino*-2-*methylthio*-5-*nitropyrimidine*, m. p. 181—183°, which become yellow in light (Found: C, 32·5; H, 3·3; N, 29·6. $C_5H_6O_2N_4S$ requires C, 32·25; H, 3·25; N, 30·1%).

4 : 5-*Diamino*-2-*methylthiopyrimidine*.—(a) *From* 4-*amino*-2-*methylthio*-5-*nitropyrimidine*. The nitro-compound (4 g.), suspended in ethanol (600 ml.), was hydrogenated (16 hr.) over 10% palladised strontium carbonate (1 g.). The filtrate was evaporated to dryness and the residue recrystallised from water (50 ml.) to give 2·4 g. of pink product (m. p. 154°). Purification as in (b) gave identical material (solubility, m. p., mixed m. p., paper chromatogram).

(b) *From* 2-*methylthiopurine*. 2-Methylthiopurine (1·5 g.) was heated with 20% aqueous dimethylamine (5 ml.) at 155—160° for 24 hr. Evaporation gave a brown residue which, crystallised (carbon) from water (8 ml.), gave a buff powder (0·6 g.; m. p. 150—155°). It was recrystallised from water (6 ml.) and then from ethyl acetate (15 ml.), giving faintly pink laths of 4 : 5-*diamino*-2-*methylthiopyrimidine* (0·3 g.), m. p. 157—159° (Found: C, 38·75; H, 5·05; N, 36·1; S, 20·45. $C_6H_8N_4S$ requires C, 38·45; H, 5·15; N, 35·9; S, 20·5%).

(c) *By methylation of* 4 : 5-*diamino*-2-*mercaptopyrimidine*. 4 : 5-Diamino-2-mercaptopyrimidine (1·4 g.) in N-potassium hydroxide (11 ml.) was shaken with methyl iodide (0·7 ml.) for 5 min., kept for 20 min. at room temperature, and refrigerated (yield 1·5 g.). Recrystallization from ethyl acetate (50 ml.) gave 1·05 g. of 4 : 5-diamino-2-methylthiopyrimidine, m. p. 157—159°.

4-*Amino*-5-*formamido*-2-*methylthiopyrimidine*.—4 : 5-Diamino-2-methylthiopyrimidine (0·8 g.) was refluxed with 98% formic acid (6 ml.) for 4 hr. The formic acid was removed in a vacuum and the residue dissolved in boiling water (30 ml.). The pH was adjusted to 5, and the solution refrigerated. The product (0·6 g.) was recrystallized from water, giving 4-*amino*-5-*formamido*-2-*methylthiopyrimidine*, m. p. 180—190° (resolidifies; see below) (Found: N, 30·75; S, 17·15. $C_6H_8ON_4S$ requires N, 30·4; S, 17·4%).

2-*Methylthiopurine* (see alternative method, above).—The above formamido-compound (0·15 g.) was heated for 5 min. after it melted (bath at 185°). The cooled residue was recrystallized from water (16 ml.), giving white needles (0·1 g.) of 2-methylthiopurine, m. p. 249—255°.

6-*Dimethylaminopurine*.—Only the hydrochloride has been described (Elion, Burgi, and Hitchings, *J. Amer. Chem. Soc.*, 1952, **74**, 411). The free base was prepared by heating 6-methylthiopurine with dimethylamine (as described for the 8-isomer, below) and also as follows. 6-Chloropurine was prepared by the action of phosphoryl chloride on 6-hydroxypurine according to an unpublished method kindly sent us by Dr. A. Bendich, and was recrystallized from water. 6-Chloropurine (0·5 g.) was heated at 100° for 1 hr. with 15% methanolic dimethylamine (11 ml.). The product was chilled and the crystals (0·32 g.) were recrystallized from alcohol (10 ml.) giving 0·22 g. of white 6-*dimethylaminopurine*, m. p. 257° (Found: C, 51·7; H, 5·5; N, 42·9. $C_7H_9N_5$ requires C, 51·5; H, 5·6; N, 42·9%). It was identical with the product made from 6-methylthiopurine (mixed m. p.; chromatogram). A further crop was obtained from the mother-liquors.

6-Methylaminopurine, prepared by the method of Elion *et al.* (*loc. cit.*), who give m. p. 312—314°, had m. p. 306°, but gave correct analyses (Found: C, 48·3; H, 4·55. Calc. for $C_6H_7N_5$: C, 48·3; H, 4·7%).

6-*Amino*-2-*hydroxypurine* (iso*Guanine*).—The sulphate (Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3113) was recrystallised from N-sulphuric acid [Found: N, 33·35; S, 7·7. Calc. for $(C_5H_5ON_5)_2,H_2SO_4,H_2O$: N, 33·45; S, 7·7%]. The base was precipitated by acetic acid from a solution of this salt (2·75 g.) in 0·25N-sodium hydroxide (110 ml.), washed well

with water, and recrystallized from water (4000 parts) as colourless needles (Found: N, 46·2. Calc. for $C_5H_5ON_5$: N, 46·35%).

8-*Phenylpurine*.—Benzoyl chloride (4·2 g., 1 equiv.) was added dropwise to 4 : 5-diaminopyrimidine (3·3 g.) in boiling anhydrous pyridine (35 ml.). Sodium hydrogen carbonate (2·52 g.) and water (15 ml.) were added to the cooled product and the whole was taken to dryness at 100°. The residue was boiled with water (350 ml.) and filtered from 4 : 5-*dibenzamidopyrimidine* (10% of pale, non-basic crystals from 13 parts of alcohol, m. p. 179°; very soluble in chloroform) (Found: C, 68·0; H, 4·4; N, 17·65. $C_{18}H_{14}O_2N_4$ requires C, 67·9, H, 4·4; N, 17·6%). The filtrate (350 ml.), concentrated to 20 ml., deposited 45% of 4-*amino*-5-*benzamidopyrimidine*, from 90 parts of water or 45 of alcohol, forming colourless crystals, m. p. 225° (Found: C, 61·6; H, 4·4; N, 26·0. $C_{11}H_{10}ON_4$ requires C, 61·7; H, 4·7; N, 26·2%). 4-Amino-5-benzamidopyrimidine (1 g.) was heated at 230° for 20 min. The residue, twice recrystallized from 33 parts of alcohol, gave 60% of colourless 8-*phenylpurine*, m. p. 261° (Found: C, 67·4; H, 4·0; N, 28·5. $C_{11}H_8N_4$ requires C, 67·3; H, 4·1; N, 28·6%).

8-*Methylpurine*.—The following method, based on Isay's process (*Ber.*, 1906, **39**, 250) gives an improved yield melting 7° higher. Acetic anhydride (25 ml.) and 4 : 5-diaminopyrimidine (5 g.) were heated to 210° during 20 min. in an open vessel under carbon dioxide, and kept at 210° (bath-temp.) for 20 min. longer. The crude product was extracted with alcohol (200 ml.), and the solution boiled with carbon (3 g.), and filtered. Concentration to 50 ml. and refrigeration gave yellow crystals which sublimed at 220°/0·01 mm. The yellow sublimate was dissolved in alcohol (500 ml.) and allowed to percolate through a column of activated alumina (2 × 8 cm.). The column was washed with a further 50 ml. The percolate and washings were evaporated to dryness (2·5 g.). The residue, recrystallized from *iso*butyl methyl ketone (550 ml.; carbon), gave white 8-methylpurine, m. p. 271—273° (Found: C, 53·65; H, 4·6. Calc. for $C_6H_6N_4$: C, 53·75; H, 4·5%).

8-*Hydroxypurine* (cf. Isay, *loc. cit.*).—Urea (7·5 g.) and 4 : 5-diaminopyrimidine (5 g.) were heated at 165° for 45 min. The crude product (4·4 g.), recrystallized twice from water (25 parts), gave white 8-hydroxypurine (2·3 g.), m. p. 305—307° (decomp.) (Found: C, 44·55; H, 3·0. Calc. for $C_5H_4ON_4$: C, 44·15; H, 2·95%).

2 : 8-*Dihydroxypurine*.—When prepared according to Johns (*Amer. Chem. J.*, 1911, **45**, 84) this was inhomogeneous (paper chromatography) and was purified by dissolution in boiling 0·4N-ammonia (100 parts; charcoal) and precipitation with acetic acid. Dried at 150° *in vacuo* it was unmelted at 350° (Found: C, 39·75; H, 2·8; N, 36·3. Calc. for $C_5H_4O_2N_4$: C, 39·5; H, 2·65; N, 36·85%).

6 : 8-*Dihydroxypurine*.—Urea (6 g.) and 4 : 5-diamino-6-hydroxypyrimidine (7·5 g.) were heated at 170° for 20 min. The cooled residue, crystallized from water (1400 ml.; insoluble residue rejected), gave 6 : 8-dihydroxypurine (3·8 g., 42%), white needles, unmelted at 350°. After recrystallization from water (330 parts) and drying at 110° it retained $0·67H_2O$, but at 160° it became anhydrous (Found: C, 39·25; H, 2·7%).

8-*Mercaptopurine*.—Isay's method (*loc. cit.*) was advantageously modified as follows. Thiourea (17 g.) and 4 : 5-diaminopyrimidine (12 g.) were heated at 195—200° for 30 min. The black residue was removed from the flask by soaking it in water (30 ml.) for 12 hr. and then extracted by boiling water (800 ml.) at pH 4—5. Treatment with carbon (10 g.) and refrigeration gave 6·9 g. of crude pink material. Three recrystallizations from water (80 parts; carbon) gave long, faintly yellow needles of 8-mercaptopurine, decomp. 300—310° (Found: S, 21·0. Calc. for $C_5H_4N_4S$: S, 21·05%).

8-*Methylthiopurine*.—8-Mercaptopurine (6·3 g.) was methylated similarly to the 2-isomer (see above). Enough water (*ca.* 200 ml.) was added to dissolve the solid at 100°. Upon refrigeration, 4·6 g. (69%) of material resulted. Recrystallization (carbon) from water (60 parts) produced white needles of 8-*methylthiopurine*, m. p. 257—259° (Found: C, 43·35; H, 3·65; S, 19·05. $C_6H_6N_4S$ requires C, 43·35; H, 3·65; S, 19·3%).

8-*Carboxymethylthiopurine*.—Crude 8-mercaptopurine (1·6 g.) and chloroacetic acid (1·2 g.) in water (50 ml.) were refluxed for 2 hr. The hot solution was brought to pH 2 and, after chilling, the solid (1·5 g.) was filtered off and dissolved in 0·1N-sodium hydroxide (100 ml.). Treatment at 60—70° with carbon, filtration, and precipitation (pH 2) with N-sulphuric acid (this cycle was repeated) gave 8-*carboxymethylthiopurine* as a white powder, decomp. slowly above 220° (Found: N, 26·75; S, 15·2. $C_7H_6O_2N_4S$ requires N, 26·7; S, 15·25%). It crystallizes (slowly) from dimethylformamide.

8-*Aminopurine*.—8-Methylthiopurine (2·5 g.) was heated with ammonia (*d* 0·89; 6 ml.), water (6 ml.), and traces of copper acetate and copper bronze at 155—160° for 24 hr. The

mixture was taken to dryness and the residue recrystallised from water (*ca.* 800 ml.), giving 1·15 g. of product. Two further recrystallizations from water (600 parts; carbon) gave small white needles of 8-*aminopurine*, m. p. $>360°$ (Found: C, 44·4; H, 3·7; N, 51·6. $C_5H_5N_5$ requires C, 44·45; H, 3·7; N, 51·8%).

8-*Methylaminopurine*.—8-Methylthiopurine (1·3 g.) was heated with aqueous methylamine (25%; 6 ml.) at 150° for 24 hr. The yellow residue after evaporation was twice recrystallized from water (60 parts), to give white 8-*methylaminopurine* (0·5 g.), m. p. 332—334° (decomp.) (Found: C, 48·6; H, 4·6; N, 47·1. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 47·0%).

8-*Dimethylaminopurine*.—8-Methylthiopurine (1·45 g.) and 20% aqueous dimethylamine (5 ml.) were heated at 140° for 24 hr. After evaporation to dryness, the residue was recrystallized from water (6 ml.) (yield 0·95 g.). Another recrystallization gave white needles of 8-*dimethylaminopurine*, m. p. 292° (decomp.) (Found: C, 51·5; H, 5·6; N, 42·9. $C_7H_9N_5$ requires C, 51·5; H, 5·6; N, 42·9%).

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Purine Studies. Part II. The Ultra-violet Absorption Spectra of Some Mono- and Poly-substituted Purines.*

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The ultra-violet absorption spectra of a number of mono- and poly-substituted purines have been measured in aqueous solution. The pH of each solution was so adjusted, by reference to the pK values of the compound studied, that simultaneous examination of more than one ionic species was avoided, as far as possible. Shifts in the wave-length and intensity consequent upon substitution are tabulated and discussed.

The ultra-violet absorption spectra of polysubstituted purines have been fairly extensively examined, but comparatively little work has been reported on monosubstituted derivatives. Much of this earlier work was carried out with solutions of arbitrary pH values, and the rest without control of pH, so that the results referred to mixtures of ions and neutral molecules uncertain in composition. In the present work the absorption spectra of each ionic and molecular species were measured, wherever possible, by using buffered solvents with pH values two units above (or below) the pK values of the compound studied. The pK_a values, the wave-lengths of maximum absorption, and the logarithms of the molecular extinction coefficients of the purines examined are recorded in Table 1, some typical absorption curves being illustrated by the Figures.

The absorption spectrum of purine resembles that of pyrimidine in aqueous solution (Boarland and McOmie, *J.*, 1952, 3716) more closely than that of glyoxaline which shows only end absorption below 260 mμ (McFarlane, *Biochem. J.*, 1936, **30**, 1199). A closer parallel exists between the spectra of the 2- or 6-monosubstituted purines and those of the corresponding 2- or 6-substituted 4 : 5-diaminopyrimidines, as has been noted (Cavalieri, Bendich, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3875) in the case of the 2 : 6-disubstituted purines and the corresponding 2 : 6-substituted 4 : 5-diaminopyrimidines. Thus 2-OH, and 2-NH_2 substituents are bathochromic and hypochromic in both the purine nucleus and 4 : 5-diaminopyrimidines, whilst 6-OH and 6-NH_2 substituents are hypsochromic and hyperchromic in those compounds. The absorption curves of the substituted purines and the correspondingly substituted 4 : 5-diaminopyrimidines resemble one another in general form and even in some detail, the curves for 2-aminopurine and 2 : 4 : 5-triaminopyrimidine both possessing shoulders at 240 mμ (Fig. 1). However, the neutral molecules of the 4 : 5-diaminopyrimidines substituted in the 6-position, and of

* Part I, preceding paper.

TABLE 1.

The values in italics refer to wave-lengths at which shoulders or inflexions occur in the absorption curves.

Substituents	Basic pK_a	Acidic pK_a	pH	Species charge	$\lambda_{max.}$ (mμ)	log ε
Purine derivatives.						
None	2·39	8·93	0·28	+	<220,[j] 260	>4·09, 3·79
			5·70	0	<220,[j] 263	>3·48, 3·90
			11·00	−	219, 271	3·92, 3·88
2-Hydroxy	1·69	8·43, 11·90	−0·75[e]	+	264, 322	3·67, 3·81
			6·05	0	238, 315	3·46, 3·69
			10·15	−	271, 313	3·68, 3·68
			13·0[f]	mainly =	219, 265, 312	4·29, 3·60, 3·83
6-Hydroxy	1·98	8·94, 12·10	−0·75[e]	+	248	4·02
			5·18	0	249	4·02
			10·35	−	258	4·05
			13·0[f]	mainly =	262	4·04
8-Hydroxy	2·58	8·24, >12	0	+	280	4·02
			5·40	0	235, 277	3·51, 4·05
			10·13	−	285	4·11
			13·0[f]	mixed − and =	284	4·10
2-Methoxy	2·44	9·2	0	+	284	3·83
			6·0	0	246, 283	3·41, 3·91
			11·4	−	283	3·88
6-Methoxy	2·21	9·16	0·20	+	254	4·01
			5·60	0	252—253	3·99
			11·3	−	261	3·99
2-Amino	3·80, −0·28	9·93	−3·5[g]	++	*235*, 325	3·81, 3·62
			1·84	+	*237*, 314	3·62, 3·60
			7·0	0	*236*, 305	3·70, 3·78
			12·0	−	*276*, 303	3·61, 3·76
6-Amino	4·22	9·8	2·10	+	262	4·12
			7·03	0	260	4·13
			12·01	−	267	4·08
8-Amino	4·68	9·36	2·40	+	288	4·20
			7·05	0	241, 283	3·51, 4·16
			12·01	−	*230*, 290	3·98, 4·07
6-Methylamino	4·18	9·99	2·02	+	267	4·18
			7·12	0	266	4·21
			12·00	−	273	4·20
8-Methylamino	4·78	9·56	2·70	+	*230*, 296	3·90, 4·24
			7·15	0	245, 290	3·50, 4·22
			12·00	−	*230*, 298	4·00, 4·16
2-Dimethylamino	4·02	10·22	1·70	+	228, *248*, 340	4·52, 3·97, 3·48
			6·98	0	223, 248, 332	4·41, 4·02, 3·71
			12·70	−	232, 327	4·39, 3·67
6-Dimethylamino	3·87	10·5	1·70	+	276	4·19
			6·98	0	275	4·25
			13·0	−	221, 281	4·21, 4·25
8-Dimethylamino	4·80	9·73	2·70	+	*230*, 305	4·04, 4·29
			7·25	0	250, 296	3·47, 4·27
			12·00	−	*230*, 306	3·91, 4·22
2-Mercapto	0·50	7·15, 10·40	−1·2[h]	+	227–232, 287, 382	3·87, 4·27, 3·26
			4·98	0	241, 285—286, 345—348	4·10, 4·25, 3·18
			8·80	−	235, 263, 328	4·12, 4·19, 3·49
6-Mercapto	<2·5[b]	7·77, 10·84	−3·5[g]	? +	225, 324	3·82, 4·17
			5·09	0	225, 325	3·87, 4·27
			9·30	−	228, 312	3·98, 4·16

TABLE 1. (*Continued.*)

Substituents	Basic pK_a	Acidic pK_a	pH	Species charge	$\lambda_{max.}$ (mμ)	log ε
8-Mercapto	<2·5 [b]	6·64, 11·16	−3·5 [g]	? +	238, *280*, 331	4·17, 3·61, 4·26
			4·50	0	231, 310	4·01, 4·46
			8·90	−	228, 313	4·13, 4·37
			13·0	=	230, 315	4·18, 4·31
2-Methylthio	1·91	8·91	0	+	241—242, *250*, 314	4·13, 4·09, 3·64
			5·90	0	232, *250*, 305	4·22, 3·93, 3·78
			11·6	−	240, 300—302	4·28, 3·79
6-Methylthio	0	8·74	−3·5 [g]	+	222, 313	4·08, 4·41
			5·80	0	*255*, 290	3·66, 4·35
			11·15	−	222, 290	4·27, 4·31
8-Methylthio	2·95	7·67	0	+	232, 305	4·04, 4·32
			5·07	0	246, 290	3·59, 4·30
			9·90	−	220, 296	4·23, 4·27
6-Methyl	2·6	9·02	0	+	265	3·88
			5·85	0	261	3·92
			11·53	−	271	3·93
8-Methyl	2·85	9·37	0	+	264	3·92
			5·85	0	266	4·01
			12·0	−	274	3·92
6-Chloro [a]	—	7·82	5·50	0	265	3·96
			10·00	−	274	3·92
8-Phenyl	2·68	8·09	0	+	237, 304	4·13, 4·41
			5·40	0	231, 298	4·06, 4·42
			10·28	−	233, 304	4·24, 4·42
2 : 6-Dihydroxy	—	7·44, 11·12	5·05	0	267	3·90
			9·99	−	240, 277	3·91, 3·92
			13·0 [f]	mainly =	283	3·94
2 : 8-Dihydroxy	—	7·45, >12	5·08	0	*230*, 310	3·90, 3·70
			10·00	−	262, 306	3·98, 3·87
			13·0 [f]	mixed − and =	220, 310	4·23, 3·98
6 : 8-Dihydroxy	—	7·65, 9·87	5·08	0	257, *280*	4·08, 3·76
			8·67	mainly [e] −	265	4·04
			12·01	=	271	4·14
6-Amino-2-hydroxy	4·51	8·99	2·00	+	*230*, 284	3·69, 4·03
			6·98	0	240, 286	3·89, 3·90
			11·14	−	*235*, 284	3·72, 4·09
2-Amino-6-hydroxy	3·3	9·2, 12·3	1·00	+	248, 271	4·03, 3·85
			6·20	0	246, 275	4·01, 3·89
			10·71	mainly [e] −	245, 273	3·78, 3·87
			13·0 [f]	mainly =	221, 274	4·12, 3·94
2 : 6-Diamino	5·09, <1·0	10·77	−1·2 [h]	partly ++	247, 296	4·01, 3·88
			3·0	+	241, 282	3·96, 4·02
			7·48	0	246—247, 279—280	3·85, 3·95
			13·0	−	*243*, 284	3·67, 3·97
2 : 6 : 8-Triamino	2·41, 6·23	10·79	0·30	++	248, 305	4·12, 4·11
			4·32	+	221, *250*, 299	4·31, 3·69, 4·24
			8·50	0	249, 293	3·80, 4·08
			13·0	−	226, 261, 295	4·31, 3·69, 4·08
2-Amino-8-phenyl	3·98	9·20	1·0	+	257, 332	4·38, 4·08
			6·50	0	238, 329	4·22, 4·28
			11·40	−	239, 330	4·31, 4·28
Pyrimidine derivatives.						
4 : 5-Diamino	6·03	—	3·20	+	284	3·94
			8·05	0	246, 289	3·89, 3·86
2 : 4 : 5-Triamino	2·56, 7·63	—	0	++	268	3·61
			5·15	+	228, *240*, 295	4·20, 4·07, 3·62
			9·80	0	232—234, 303	3·92, 3·73

TABLE 1. (*Continued.*)

Substituents	Basic pK_a	Acidic pK_a	pH	Species charge	$\lambda_{max.}$ (mμ)	log ε
4 : 5 : 6-Triamino	1·47, 5·78	—	−0·75 [a]	++	265	4·01
			3·55	+	287	4·01
			7·98	0	277, 380	3·89, 2·37
4 : 5-Diamino-2-hydroxy ...	4·37	11·45	2·30	+	305	3·76
			6·98	0	292	3·58
			13·0	−	226, 303	3·91, 3·67
4 : 5-Diamino-6-hydroxy ...	1·34, 3·57	9·86	−0·75 [a]	++	257	3·85
			2·45	+	258	3·74
			6·70	0	278, 372	3·95, 2·44
			12·00	−	272, 370	3·87, 2·62
4 : 5-Diamino-2-mercapto ...	2·96	10·39	1·0	+	231, 293, *338*	3·96, 4·28, 3·68
			6·50	0	*250*, 271, *335*	4·19, 4·22, 3·26
			12·40	−	221, 269, 316	4·17, 4·17, 3·71
Various compounds.						
S-Methyl*iso*thiourea	9·83 [b]	—	7·05	+	220	4·58
			12·0	0	238	3·74
Thiourea	*ca.* −1 [c]	—	7·05	0	236	4·08
O-Methyl*iso*urea	9·80 [d]	—	7·50	+	<220	>0·48
			12·0	0	<220	>1·43
Benzamidine	11·6 [d]	—	7·00	+	268, 229	2·91, 3·96
			13·00	0	228	3·93
Acetamidine	12·52 [d]	—	7·00	+	<220	>1·58
			13·0 [f]	mainly 0	219	3·04
Acetylguanidine	8·33 [d]	—	6·05	+	220	2·76
			10·5	0	229	4·14

[a] The basic pK_a and the absorption spectrum of the cation were not measurable owing to hydrolysis in acid solution. [b] The basic pK_a was not determinable, either potentiometrically or spectroscopically. [c] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [d] Walker, *Z. physikal. Chem.*, 1889, **4**, 319. [e] 4N-Sulphuric acid. [f] The highest pH used with silica absorption cells. [g] 13·5N-Sulphuric acid. [h] 5N-Sulphuric acid. [i] The two acid dissociation constants are too close together to permit the examination of the spectrum of the mono-anion. [j] The wave-length of maximum absorption of the *y* band in the spectra of many purines lies below 220 mμ and so cannot be measured with accuracy. The logarithm of the molar extinction coefficient at 220 mμ is tabulated only in the cases of the purine cation and the purine neutral molecule.

4 : 5-diaminopyrimidine itself, give rise to a band at 370—380 and 246 mμ respectively which disappears on cation formation, a phenomenon which is not observed in the case of any of the purine derivatives examined. Such a band may be due to an $n \longrightarrow \pi$ forbidden transition in the case of the 6-substituted 4 : 5-diaminopyrimidines as it is only of moderate intensity (ε 300) in the spectra of these compounds (Platt, *J. Opt. Soc. Amer.*, 1953, **43**, 252), whilst in the case of 4 : 5-diaminopyrimidine itself, where the intensity of the band is higher (ε 7700), it may be due to the conjugation of an amino-group with the pyrimidine nucleus, a conjugation which is destroyed by cation formation.

The ultra-violet absorption spectra of the substituted purines consist in general of two broad bands. These lie at 260 and <220 mμ in the case of the purine molecule itself, and may be designated the *x*, and the *y* band respectively. The corresponding molecules with fewer, or no, nitrogen atoms in the nucleus give rise to three distinct bands in the same region, and so too does 9-methylpurine when examined in *cyclo*hexane, this compound being the only purine that could be studied in a non-polar solvent (Table 2). The introduction of a nitrogen atom into the *cyclo*pentadiene ring of indene brings about a marked increase in the intensity of the first (longest-wave-length) band, and a decrease in that of the second, no great intensity changes being brought about in these bands by the substitution of further nitrogen atoms in this ring (Table 2). The introduction of a nitrogen atom into the benzene ring of benziminazole causes a further increase in the intensity of the first band and a further decrease in that of the second, the substitution of another nitrogen atom into this ring again causing no great intensity changes in these

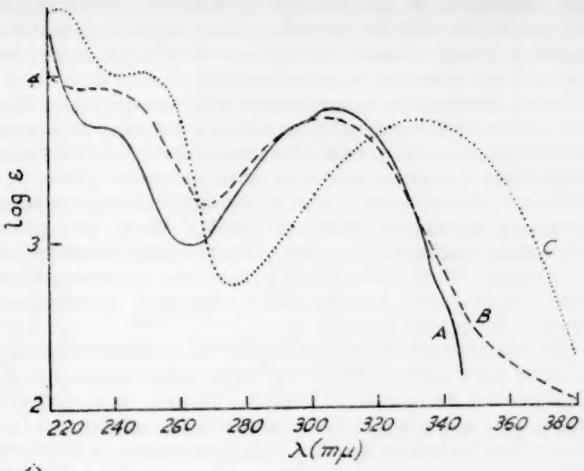


FIG. 1.

2-Aminopurine:
A, neutral molecule.
2 : 4 : 5-Triaminopyrimidine:
B, neutral molecule.
2-Dimethylaminopurine:
C, neutral molecule.

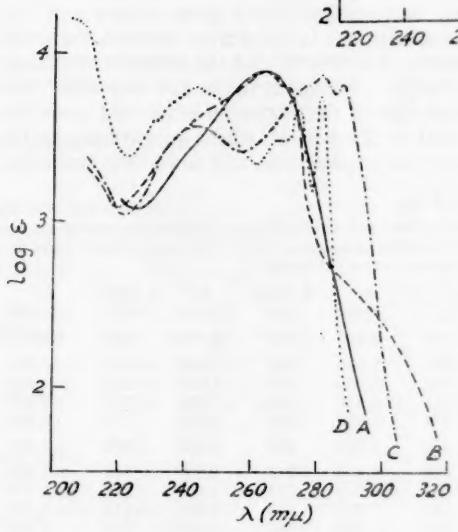


FIG. 2.

9-Methylpurine:
A, neutral molecule (pH 5·05).
B, in cyclo*hexane.*
1 : 3 : 4-Triazaindene:
C, in cyclo*hexane.*
Benziminazole:
D, in cyclo*hexane.*

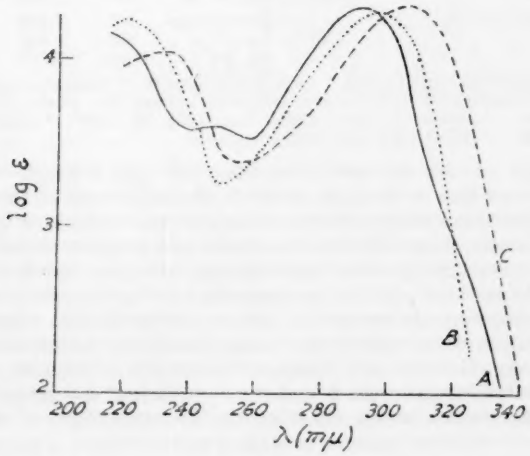


FIG. 3. *8-Methylthiopurine*:
A, neutral molecule.
B, anion.
C, cation.

bands. However, in the spectrum of 9-methylpurine in *cyclo*hexane these two bands lie close together, so that the second appears only as a shoulder on the short-wave side of the first, and in the spectrum of this compound in aqueous solution, these two bands appear to be merged under a common envelope (Fig. 2).

Thus it seems, from a comparison with the spectra of the azaindenes, that the *x* band in the spectra of the purines is an envelope covering two transitions, the first more intense than the second. The spectra of indene and indole have been placed on a sequence linking the spectrum of styrene with that of naphthalene (Platt, *J. Chem. Phys.*, **1951**, **19**, 101), the first two transitions of both styrene and naphthalene being longitudinal and transverse respectively (*idem*, *ibid.*, 1950, **18**, 1168). Hence it is probable that the *x* band in the spectra of the purines is due principally to a longitudinal polarization of the purine nucleus with a smaller contribution from a transverse polarization, making the band composite in nature. Such a view is supported by the effect of substituents upon the position of the *x* band in the purine spectra.

The changes in the wave-lengths of maximum absorption and in the molecular extinction coefficients induced by single substituents placed in different positions of the purine nucleus are given in Table 3. It may be seen that, for a given substituent, the changes vary according to the position of the substituent in the purine nucleus, the order of increasing bathochromic shift being, in general, $6 < 8 < 2$, and the order of increasing hyperchromic effect, $2 \ll 6 \ll 8$, for the *x* bands. Substituents in the 6-position are transversely disposed with respect to the longer axis of the purine molecule and lower the transition energy only of the weaker component of the *x* band, whilst substituents in the 8-position are longitudinally disposed with respect to that axis and lower the transition

TABLE 2.

The values of the wave-length of maximum absorption and the molecular extinction coefficient are taken from the smooth curve drawn through the vibrational fine structure in the cases where such fine structure was observed. Values in italics refer to shoulders or inflexions.

Compound	pK_a	Solvent	λ_1 (mμ)	ε_1	λ_2 (mμ)	ε_2	λ_3 (mμ)	ε_3
Indene [a]	—	*n*-Hexane	280	500	250	10,000	220	20,000
Indole [a]	—	*cyclo*Hexane	280	4,000	265	6,500	219	25,000
Benziminazole [b]	—	*cyclo*Hexane	275	3,800	243	6,200	<210	>12,000
	5·53 [d]	Aq. pH 2·0	268	5,500	*240*	3,800	<210	>8,300
	—	Aq. pH 9·1	271	4,250	244	5,100	<220	>2,000
	12·3 [d]	Aq. pH 13 [e]	274	5,400	250	3,600	217	6,900
Benzotriazole [c]	—	*iso*Octane	278	4,800	248	6,000	<220	>1,500
1 : 3 : 4-Triazaindene [b]	—	*cyclo*Hexane	282	6,900	243	3,600	<210	>2,400
	3·95	Aq. pH 1	282	8,300	231	1,800	<210	>2,700
	—	Aq. pH 7	282	9,500	244	3,380	<210	>2,800
	11·08	Aq. pH 13	289	10,000	*265*	3,600	218	3,300
9-Methylpurine [b]	—	*cyclo*Hexane	263	7,600	*240*	3,700	<210	>2,000
	2·36	Aq. pH 0	262	5,500	—	—	<220	>8,400
	—	Aq. pH 5	264	7,700	—	—	<220	>1,300

[a] Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Wiley & Sons, New York, and Chapman & Hall, London, 1951, Nos. 189 and 192; Platt, *J. Chem. Phys.*, **1951**, **19**, 101. [b] Present work. [c] Ewing, *J. Amer. Chem. Soc.*, 1951, **73**, 4360. [d] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [e] Highest pH used with silica cells.

energy of the stronger component of the *x* band. Substituents in the 2-position are orientated at an angle of 30° to the longer axis of the purine molecule and thus lower the transition energy of both of the components making up the *x* band. In benziminazole and indole, where the first two transitions give rise to distinct absorption bands, a methyl group has the greatest bathochromic effect on the first (longitudinal) transition when placed in the 6-position, corresponding to the 2-position in purine, whilst a methyl group in benziminazole exerts the greatest hyperchromic effect upon the second (transverse) transition when substituted in the 4-position, corresponding to the 6-position in purine (Beaven, Holiday, and Johnson, *Spectrochim. Acta*, 1951, **4**, 338).

Substituents in the 2- and the 8-position of the purine nucleus appear in some cases to exert a bathochromic effect on the first transition of the purine spectrum sufficient to separate the two transitions making up the *x* band of purine itself. The neutral molecules

of purines substituted in the 8-position by groups carrying unshared electrons show small peaks at 235—250 mμ, of molecular extinction coefficient 2900—3900, in all of the cases studied save 8-mercaptopurine, where there is but a slight shoulder at 240 mμ which is overshadowed by the *y*-band peak at 231 mμ. Similar peaks are found in the spectra of purines substituted in the 2-position by groups carrying unshared electrons, but here such peaks, whilst present predominantly in the spectra of the uncharged species, are found also in the spectra of some cationic, and some anionic forms, and they vary much more widely in intensity (ε 2500—10,500). These peaks are not due to the absorption of radiation by the substituted amidine chromophore (–N:CX–N=, where X = OH, OMe, SH, SMe, NH_2, NHMe, NMe_2), a grouping common to the 2- and the 8-substituted purines, for, of the substituted amidines studied (Table 1), only thiourea and *S*-methyl*iso*thiourea gave absorption bands in the required region.

TABLE 3.

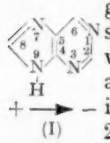
The shifts are measured relative to the corresponding ionic species of purine.

		Position of substituent					
		2	6	8	2	6	8
		Shift in wave-length of the *x*-band (mμ)			Shift in mol. extinction coefficient (× 10^{-3})		
Substituent	Species						
Amino	+	54	2	28	−2·18	7·11	10·02
	0	42	−3	20	−1·92	5·61	6·45
	−	32	−4	19	−1·83	4·53	4·17
Methylamino	+	—	7	36	—	8·98	11·22
	0	—	3	27	—	8·28	8·66
	−	—	2	27	—	8·27	6·87
Dimethylamino	+	80	16	45	−3·12	9·47	13·34
	0	69	12	33	−2·85	9·68	10·68
	−	56	10	35	−2·95	10·20	9·02
Hydroxy	+	62	−12	20	0·29	4·31	4·19
	0	52	−14	14	−3·04	2·53	3·28
	−	42	−13	14	−2·57	3·64	5·30
Methoxy	+	24	− 6	—	0·55	4·07	—
	0	20	−10	—	0·09	1·85	—
	−	14	−10	—	−0·07	2·33	—
Mercapto	+	122	66	70	−4·34	10·44	13·79
	0	84	62	47	−6·44	10·68	20·90
	−	57	41	42	−4·51	6·87	15·86
Methylthio	+	54	53	45	−1·80	19·54	14·73
	0	42	27	27	−2·06	14·45	14·45
	−	29	19	25	0	12·84	11·04
Methyl	+	—	5	4	—	1·42	2·15
	0	—	−2	3	—	0·37	2·29
	−	—	0	3	—	0·93	0·73
Phenyl	+	—	—	44	—	—	19·25
	0	—	—	35	—	—	18·42
	−	—	—	33	—	—	18·66
Chloro	0	—	2	—	—	1·85	—
	−	—	3	—	—	0·77	—

It is probable that these small peaks are the second transition contributing to the composite *x* band of the purine spectrum, as they approximate in position and intensity to the second band observed in the spectrum of 9-methylpurine in *cyclo*hexane solution (Table 2) in the case of the 8-substituted purines. Here the substituents are orientated along the longitudinal axis of the purine molecule, so that they do not greatly affect the position and intensity of the second transition, which is transverse, whilst they bring about a marked bathochromic shift of the first transition, which is longitudinal, separating it from the second. Similar considerations apply to substituents in the 2-position of purine, though these, being orientated at an angle of 30° to the longitudinal axis of the molecule, exert a greater influence on the second transition, as may be seen from the wider variation in the intensity of the bands between 235 and 250 mμ in the spectra of the 2-substituted purines.

It is noteworthy that the second transition of the purine spectrum appears as a distinct band predominantly in the spectra of the neutral molecules of 2- and 8-substituted purines, in fact, exclusively so in the case of the 8-substituted purines. The second transition of the spectral sequence connecting benzene with naphthalene, to which the spectrum of purine is linked through the azaindenes, has been analysed as a transition to a multipolar excited state with wave-function antinodes at the ring atoms (Klevens and Platt, *J. Chem. Phys.*, 1949, **17**, 470; Platt, *ibid.*, 1949, **17**, 484; 1951, **19**, 101). Accordingly this transition is particularly sensitive to perturbations, and it is likely that anion or cation formation in 2- and 8-substituted purines displaced this transition into the envelope of one or other of the more intense bands on either side. In the spectrum of 1 : 3 : 4-triazaindene the band of the second transition, which is distinct in the neutral molecule, is much reduced in intensity and is markedly displaced towards shorter wave-lengths in the cation, whilst in the anion it is greatly displaced towards longer wave-lengths and is almost completely merged into the band of the first transition. In the case of 9-methylpurine even the change from a non-polar to a polar solvent brings the first and the second transition of the spectrum of the neutral molecule under a common envelope.

The intensity changes caused by a substituent in the first band of the spectra of benzenoid ring systems have been shown to be proportional to the "spectroscopic moment" of the substituent, a parameter which may be loosely correlated with the mesomeric moment of the substituent and its directing power (Platt, *ibid.*, 1951, **19**, 263; and earlier references quoted by this author). The stronger transition of the purine *x* band corresponds to the first band of the spectra of benzenoid ring systems according to the sequence drawn up by Platt (see p. 2076), and some indication of the effect of substituents on the intensity of the *x* band of purine may be given in terms of their mesomeric effect on the separation of charge in the purine nucleus. Glyoxaline, benziminazole, and purine form a series of diminishing basic strength and increasing acid strength (Albert, Goldacre, and Phillips, *J.*, 1948, 2240; also Part I), indicating that the benzene, and more particularly the pyrimidine, nucleus exerts an electron-withdrawing effect on the glyoxaline ring, giving rise to longitudinal dipole (I). Electron-donating substituents, by virtue of their mesomeric effect, would enhance this dipole when placed in the 8-position and diminish it when placed in the 2-position, an observation which helps to explain the hyperchromic effect of substituents in the 8-position, and the hypochromic effect of substituents in the 2-position of the purine nucleus. Similarly, such substituents in the 6-position would enhance, and in the 2-position would diminish, a transverse dipole across the pyrimidine ring of the purine nucleus caused by the electron-attracting property of the aza-nitrogen atoms of that ring, substituents in the 6-position being hyperchromic, and in the 2-position being hypochromic, in conformity with this view.



(I)

Substituents in the 2-position of the purine nucleus exhibit the following order of increasing bathochromic shift, the same order being observed with the anions and cations as with the neutral molecules: MeO < MeS ≪ NH_2 < HO < NMe_2 < HS. With substituents in the 6- and the 8-position the orders of increasing bathochromic effect vary somewhat from one species to another. In the 6-position some substituents are bathochromic and others hypsochromic. For the neutral molecules the order of increasing bathochromic shift may be written: Cl < NHMe < NMe_2 < MeS < HS, and the order of increasing hypsochromic effect: Me < NH_2 < MeO < HO. The neutral molecules of the 8-substituted purines may be placed in the following order with regard to increasing bathochromic shift: Me < HO < NH_2 < MeHN = MeS < NMe_2 < Ph < HS.

The *y* (short-wave) bands of the absorption spectra of the substituted purines lie, in general, at too short a wave-length to be measured with accuracy, save in the cases of the purine anion and the anions of a number of monosubstituted purines. With the results from these cases the effect of substituents in the purine nucleus on the *y* band can be indicated to some degree. Substituents in the 2-position exert a bathochromic effect, increasing in the order: MeO < NMe_2 < MeS < HS < HO < NH_2. Substituents in the 6-position tend in general to bring about a hypsochromic shift in the *y* band; so do substituents in the 8-position, in contrast to their effect upon the *x* band.

The above series do not necessarily express the true order of the bathochromic effect of substituents on the purine spectrum, as it is possible that potentially tautomeric substituents exist in their corresponding oxo-, thiono-, or imino-forms, giving rise to different chromophore systems. It has been shown theoretically that such tautomers may give the same spectrum as the true hydroxy-, mercapto-, or amino-forms (Brown and Lahey, *Austral. J. Sci. Res.*, 1950, **3**, 615), but for comparison with other chromophore systems only the order of the bathochromic effect of non-potentially tautomeric substituents will be considered here, apart from the amino-group which appears to exist in the true amino-form (see below). The order of the bathochromic effects of substituents in the 2- and the 8-position on the *x* band of the purine spectrum resembles that of the effect of the same auxochromes on the 250-mμ band of benzene, a band related by a spectral sequence with the stronger transition of the purine *x* band (see above). The magnitude of the bathochromic shifts induced by the substituents in the 2-position are somewhat greater, and in the 8-position somewhat less, than the shifts induced by the same substituents in the benzene ring (Bowden and Braude, *J.*, 1952, 1068), an observation which may be related to the greater polarizability of the pyrimidine ring, and the smaller

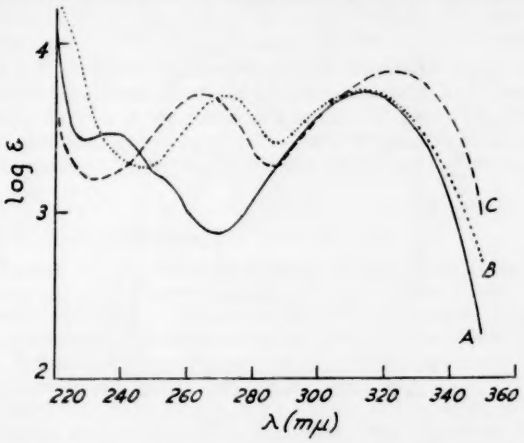


FIG. 4. *2-Hydroxypurine*:
A, neutral molecule.
B, anion.
C, cation.

polarizability of the glyoxaline ring in the purine nucleus, which is to be expected from the migration of π-electrons from the glyoxaline ring to the pyrimidine ring in purine.

Of the shifts induced in the *x* band of the purine spectrum by substituents in the 6-position those which are bathochromic follow the order observed with the ethylenic chromophore, though they are smaller, whilst those that are hypsochromic follow the order found in the C:C·C(X):O system (Bowden, Braude, and Jones, *J.*, 1946, 948). Substituents in the 6-position of purine form the C:C·C(X):N system with part of the pyrimidine ring, a system which might be expected to be intermediate in spectroscopic properties between the corresponding enone and diene chromophores.

In the di- and tri-substituted purines, the effect of the individual substituents on either the wave-length of maximum absorption or the molecular extinction coefficient is not additive even where there is not more than one potentially tautomeric substituent in the purine nucleus. Additivity has been observed for disubstituted pyrimidines containing not more than one potentially tautomeric group (Boarland and McOmie, *J.*, 1952, 3722), indicating a lack of interaction between the two substituents. Thus it seems that there is some conjugation between the substituents of a di- or tri-substituted purine. An amino- or hydroxy-group introduced into the 6-position of an 8- or 2-substituted purine brings about a greater hypsochromic shift than it does in the case of the purine molecule itself, whilst such a group introduced into the 2-position of a 6- or an 8-substituted purine gives rise to a smaller bathochromic shift than it does in the parent molecule. A hydroxyl group placed in the 8-position of a 2- or 6-substituted purine produces no very great changes

in wave-length of maximum absorption, but a phenyl group introduced into the 8-position of such a substituted purine gives rise to marked bathochromic shifts, though these shifts are smaller than those observed on substitution of the parent molecule with an 8-phenyl group.

The spectra of the amino- and hydroxy-purines might be expected to afford some indication of the structures of their ions as the NH_3^+ group should exert the same bathochromic effect as the H or CH_3 group, owing to the fixation of the unshared electrons of the nitrogen atom in the cationic form, whilst the O^- group should exert the same bathochromic effect as the NH_2 group, owing to the similar polarizabilities of those groups (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127).

The presence of an NH_3^+ group in *N*-heteroaromatic molecules has not yet been demonstrated, and in the one case where the spectrum of the cationic form of an aminopurine resembles that of the neutral molecules of the corresponding methyl derivative (6-aminopurine cation, $\lambda_{max.}$ 262 mμ, and 6-methylpurine neutral molecule, $\lambda_{max.}$ 261 mμ), it is known from crystallographic evidence that the cationic proton of the aminopurine is attached to the 1-nitrogen atom of the purine nucleus (Cochran, *Acta Cryst.*, 1951, **4**, 81). The spectrum of the anionic form of 6-hydroxypurine resembles that of the neutral

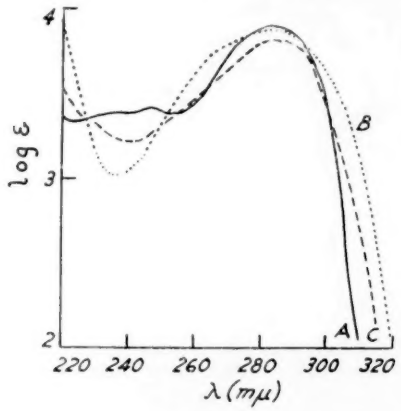
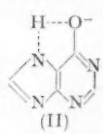


FIG. 5. *2-Methoxypurine:*
A, neutral molecule.
B, anion.
C, cation.

molecule of 6-aminopurine ($\lambda_{max.}$ 258 and 260 mμ respectively), but the spectra of the 2-hydroxy- and 8-hydroxy-purine anions differ from those of the neutral molecules of the corresponding aminopurines (Figs. 1 and 4). Thus it is probable that anion formation in the 2-hydroxy- and 8-hydroxy-purine involves the dissocation of a proton from a nitrogen atom of the glyoxaline ring, not from the hydroxyl group. In the case of 6-hydroxypurine there is some evidence that the first acidic dissociation constant belongs to the hydroxyl group (Albert, *Biochem. J.*, 1953, **54**, 646). Here the same anion could be formed whether the proton dissociated from the hydroxyl group or the imino-group of the glyoxaline ring, the oxygen atom substituted in the 6-position and the nitrogen atom in the 7-position being linked by a hydrogen bond in the anion (II). In 6-aminopurine also there is some evidence of hydrogen bonding between the substituent and the 7-nitrogen atom of the purine nucleus, at least in the cation (Cochran, *loc. cit.*), an observation indicating a similarity between the structures of the 6-hydroxypurine anion and 6-aminopurine which helps to explain the resemblance of their spectra.



(II)

The hydroxy-, mercapto-, and amino-purines may possibly exist, wholly or in part, in their corresponding tautomeric forms. Some indication of the nature of such potentially tautomeric groups substituted in the purine nucleus may be obtained from comparisons between the spectra of such purines and those of the corresponding methoxy-, methylthio-, and dimethylamino-purines. However, such indications can only be tentative in the present work as comparisons with the spectra of the corresponding *N*-methyl-oxo-, -thiono-,

and -imino-purines would be required for definitive assignments of structure. The spectra of all the monoaminopurines resemble those of the same ionic forms of the corresponding dimethylamino-derivatives (Fig. 1), suggesting that the amino-purines exist predominantly in the true amino-form. The spectra of 6-hydroxypurine, too, are similar to those of the corresponding ionic forms of 6-methoxypurine, but there are considerable differences between the spectral absorption curves given by 2-hydroxypurine and 2-methoxypurine (Figs. 4 and 5). These observations neither prove nor exclude the possibility that 6-hydroxypurine exists principally in the hydroxy-form, as cases are known in other *N*-heteroaromatic structures where the spectrum of a hydroxy-derivative resembles the spectra of both the corresponding methylated tautomers (Albert, Brown, and Cheeseman, *J.*, 1952, 4219). However, the differences between the spectra of 2-hydroxy- and 2-methoxy-purine strongly suggest that 2-hydroxypurine exists principally in the keto-form.

With regard to the sulphur-substituted purines, the spectra of all the mercaptopurines differ from those of the same ionic forms of the corresponding methylthiopurines, the differences being the most prominent with the 2-substituted derivatives and least marked with the 6-substituted derivatives. Thus it is possible that 2-mercaptopurine, at least, exists to some extent in the thiono-form, this being the more probable because all the ionic forms of 2-mercaptopurine exhibit absorption peaks at 330 mμ or longer wavelengths, a region in which the C:S group shows an absorption maximum (Braude, *Ann. Reports*, 1945, **42**, 112). However, the intensities of the peaks in the spectra of 2-mercaptopurine are rather high (ε 2—20 $\times$ 10^3) for a spin-forbidden transition of the type found in the 330-mμ band of the thione chromophore (ε *ca.* 5), though it is possible that intensity is " borrowed " from the neighbouring high-intensity *x* band of the purine absorption in the case of 2-mercaptopurine.

Experimental

Source of Materials.—The sources of the purine derivatives studied were as in Part I. 4 : 5-Diaminopyrimidine was prepared according to Brown (*J. Appl. Chem.*, 1952, **2**, 239), 4 : 5-diamino-2-mercaptopyrimidine according to Elion and Hitchings (*J. Amer. Chem. Soc.*, 1947, **69**, 2553), 4 : 5-diamino-2-hydroxypyrimidine according to Johns (*Amer. Chem. J.*, 1911, **45**, 79), and 2 : 4 : 5- and 4 : 5 : 6-triaminopyrimidine and 4 : 5-diamino-6-hydroxypyrimidine according to Albert, Brown, and Cheeseman (*J.*, 1951, 474).

Benziminazole and thiourea specimens from British Drug Houses Ltd. were recrystallized.

1 : 3 : 4-Triazaindene was prepared according to Kögl (*Rec. Trav. chim.*, 1948, **67**, 29).

O-Methylurea hydrochloride was kindly supplied by Dr. E. Hoerger (Talladega College, Talladega, Alabama).

Acetylguanidine was prepared according to Traube (*Ber.*, 1910, **43**, 3586), benzamidine according to Pinner (" Die Imidoäther und ihre Derivate," R. Oppenheim, Berlin, 1892, p. 152 ff.), *S*-methyl*iso*thiourea sulphate according to *Org. Synth.*, Coll. Vol. II, p. 411, and acetamidine hydrochloride according to *Org. Synth.*, 1928, **8**, 1.

Absorption Spectra.—These were measured with a Hilger Uvispek H700/301 Quartz Spectrophotometer, with buffer solutions with the pH values recorded in Table 1. The buffer solutions were 0·01M-glycine (for pH 1·5—3·5), 0·01M-acetate (for pH 3·8—5·7), 0·01M-phosphate (for pH 6·0—7·9, and pH 10·3—11·3), 0·01M-borate (for pH 8·2—10·0), together with N- (pH 0) and 0·1N-hydrochloric acid (pH 1·0), and 0·1N- (pH 13) and 0·01N-potassium hydroxide (pH 12).

pK_a *Determinations.*—The pK_a values of 1 : 3 : 4-triazaindene and of the 2- and the 6-substituted 4 : 5-diaminopyrimidines were determined by potentiometric titration of 0·01M-aqueous solutions with a glass electrode and a Cambridge pH meter. The pK_a values recorded in Table 1 are correct within $\pm$0·08 pH unit.

The author thanks Mr. E. P. Serjeant for help with the spectroscopy and potentiometry, and Mr. D. Light also with respect to the latter.

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The Reactions of Amines and Sulphur with Olefins. Part I. The Reaction of Diethylamine and Sulphur with cyclo*Hexene.*

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The reaction of diethylamine and sulphur with *cyclo*hexene at 140° yields di*cyclo*hexyl mono- and di-sulphides and saturated polymeric products, $C_6H_{11}\cdot S_x\cdot(C_6H_{10})\cdot S_x\cdot C_6H_{11}$, containing *cyclo*hexane units linked by sulphur, where x is 1 or 2. *N*-Ethylthioacetamide (IV) is formed as a major product, and minor products include *NN*-diethylthioacetamide (V) and diethylammonium hydrogen sulphide (VI); (IV)—(VI) are also formed by reaction of diethylamine with sulphur at 140°. The mechanisms of the olefin–sulphuration processes are discussed.

One of the main objectives of the work described in this group of papers is the utilisation of combinations of amine and sulphur to effect the sulphuration of mono- and $\Delta^{1:5}$-di-olefins. Examination of the rôle of the amine in determining the structural types of the sulphur linkages in the sulphurated product is of importance since upon such studies must be based a clearer understanding of the function of amines and derived basic compounds as accelerators of sulphur vulcanisation.

The formation of complexes between sulphur and secondary amines at room temperature was reported by Bedford (*India Rubber World*, 1921, **64**, 572; U.S.P. 1,719,920/1929) and by Levi (*Gazzetta*, 1930, **60**, 975; 1931, **61**, 286). It has now been found that treatment of such complexes with polar solvents, such as ethanol, *quantitatively* liberates the sulphur in an active form which converts sodium sulphite into thiosulphate at room temperature. Analogous behaviour is the action of piperidine at room temperature on variously constituted dialkyl tetrasulphides in removing a considerable proportion of the polysulphidic sulphur in the form of the complex, the tetrasulphide being largely converted into disulphide. Several workers (Kratz, Flower, and Coolidge, *Ind. Eng. Chem.*, 1920, **12**, 317; Bedford and Scott, *ibid.*, 1921, **13**, 126) have suggested that the accelerating effect of amines in rubber vulcanisation is due to the thermal liberation of active sulphur. However, attempts to sulphurise *cyclo*hexene at 60—80° with the complexes from sulphur and various secondary amines proved unsuccessful, and it thus seems unlikely that liberation of active sulphur under these conditions is occurring. Attention was therefore directed to the sulphuration capabilities of the amine–sulphur combination at 140°.

Reaction of *cyclo*hexene with diethylamine and sulphur at 140° gave a high yield of sulphurated products which consisted mainly of di*cyclo*hexyl monosulphide, together with a smaller amount of the disulphide; *cyclo*hexanethiol and di*cyclo*hexyl polysulphides having three or more sulphur atoms in the cross-link were formed in negligible amount. A mixture of saturated polymeric products containing three or more *cyclo*hexane units linked by mono- or di-sulphide bridges, *e.g.*, $C_6H_{11}\cdot S_{1-2}\cdot C_6H_{10}\cdot S\cdot C_6H_{11}$ (I), was also obtained, and identified by elementary and infra-red spectroscopic analysis, by molecular-weight determination, and by examination of the products resulting from its reduction with lithium aluminium hydride (Arnold, Lien, and Alm, *J. Amer. Chem. Soc.*, 1950, **72**, 731). This treatment gave *cyclo*hexanethiol, a thiol sulphide, $C_6H_{11}\cdot S\cdot C_6H_{10}\cdot SH$ (II), and an unreducible polymeric material containing monosulphide bridges, *viz.*, $C_6H_{11}\cdot S\cdot C_6H_{10}\cdot S\cdot C_6H_{11}$ (III). There was no evidence for the presence in the reduction product of *cyclo*hexanedithiol which would have resulted from a polymer of the type $C_6H_{11}\cdot S_2\cdot C_6H_{10}\cdot S_2\cdot C_6H_{11}$. It is noteworthy that a sulphurated polymer, obtained from unaccelerated sulphur–olefin interaction, was reported by Armstrong, Little, and Doak (*Ind. Eng. Chem.*, 1944, **36**, 628) but was not examined.

The fully saturated and predominantly mono- and di-sulphidic nature of the present products contrasts markedly with the apparent alkyl alkenyl nature of the polysulphide obtained by Farmer and Shipley (*J.*, 1947, 1519) from the reaction of sulphur with *cyclo*hexene at 140° (cf. Selker and Kemp, *Ind. Eng. Chem.*, 1947, **39**, 895). On the other hand,

the present results recall the work of Naylor (*J.*, 1947, 1532) who found that polar addition of hydrogen sulphide to mono-olefins at 140° gave alkanethiols and alkyl mono- and di-sulphides, though in yields considerably inferior to those now obtained.

Sulphurated nitrogenous compounds, derived from the reaction of diethylamine and sulphur, were isolated and characterised as *N*-ethylthioacetamide (IV), *NN*-diethylthioacetamide (V), and diethylammonium hydrogen sulphide (VI), the last two compounds being isolated in minor amounts only. The possible formation of *NN'*-thiobisdiethylamine, $S(NEt_2)_2$ (VII), and of the corresponding polysulphides was ruled out since an authentic sample of (VII) readily formed a crystalline, water-soluble thionate with sulphurous acid (Lecher, Weigel, and Wittner, G.P. 517,995/1927), whereas this reagent failed to remove the nitrogenous component from the di*cyclo*hexyl sulphide fractions. Infra-red spectroscopic examination also failed to reveal the presence of any *NN'*-thioamines $(Et_2N)_2S_x$. The existence of both thione and thiol forms of (IV), $CH_3{\cdot}CS{\cdot}NHEt$ and $CH_3{\cdot}C(\cdot SH){:}NEt$, suggested the possible formation of the *cyclo*hexylthio-derivative, $CH_3{\cdot}C(:NEt){\cdot}S{\cdot}C_6H_{11}$, by reaction of (IV) with *cyclo*hexene, but no evidence of such addition was found. Similarly, diethyl*cyclo*hexylamine was not formed when diethylamine was heated with *cyclo*hexene at 140°, in contrast to the known addition of amines to activated double bonds (Bieber, *Compt. rend.*, 1950, **231**, 291).

Independent investigation of the reaction of diethylamine and sulphur at 140° revealed that both (IV) and (VI) were major products, formed by replacement of the α-methylenic hydrogen atoms of the amine by sulphur, as represented formally by (1) :

$$CH_3{\cdot}CH_2{\cdot}NHEt + 2S \longrightarrow H_2S + CH_3{\cdot}CS{\cdot}NHEt \quad (IV) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

A minor product of this reaction was (V), whose formation is attributed to the alkylation process (2). This compound also resulted from the reaction between sulphur and triethylamine at 140° (cf. Levesque, U.S.P. 2,560,296/1951).

$$NHEt_2 + CH_3{\cdot}CS{\cdot}NHEt \longrightarrow NH_2Et + CH_3{\cdot}CS{\cdot}NEt_2 \quad (V) \quad . \quad . \quad . \quad . \quad (2)$$

Mechanism of the cyclo*Hexene Sulphuration Reaction.*—It is considered that a major sulphurating agent in the reaction at 140° of diethylamine and sulphur with *cyclo*hexene is diethylammonium hydrogen sulphide (VI). Polar addition of (VI) to the olefin gives *cyclo*hexanethiol, which then undergoes : (i) further polar addition to give di*cyclo*hexyl monosulphide, and (ii) base-catalysed oxidation by sulphur to give di*cyclo*hexyl di- and poly-sulphides and more hydrogen sulphide, a reaction known to be rapid even at room temperature (Bloomfield, *J. Soc. Chem. Ind.*, 1948, **67**, 14; McMillan and King, *J. Amer. Chem. Soc.*, 1948, **70**, 4143) :

$$C_6H_{10} + \underset{\text{(VI)}}{NH_2Et_2^+}SH^- \longrightarrow C_6H_{11}{\cdot}SH \xrightarrow[(i)]{C_6H_{10}} C_6H_{11}{\cdot}S{\cdot}C_6H_{11} \quad . \quad . \quad (3)$$

$$C_6H_{11}{\cdot}SH \xrightarrow{(ii)\ S\text{–Base}} C_6H_{11}{\cdot}S_x{\cdot}C_6H_{11}$$

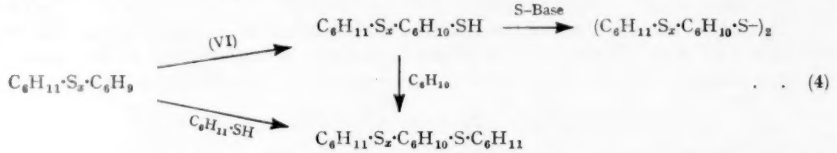
Compelling evidence for the ionic course of these reactions is presented in Part II (following paper), where it is shown that the thiols and sulphides obtained from the comparable sulphuration of trialkylethylenes invariably have a *tert.*-alkyl configuration.

The absence of *cyclo*hexanethiol, in contrast to the results of Naylor (*loc. cit.*), and the isolation of a considerable proportion of the monosulphide indicate the ease with which path (i) is followed. This was initially considered to be due to base catalysis of addition of hydrogen sulphide and thiol to the olefin, especially since such catalysis has already been observed (Foldi and Kollonitsch, *J.*, 1948, 1683; Dahlbom, *Acta Chem. Scand.*, 1951, **5**, 690). However, this explanation is inadequate since reaction of (VI) with *cyclo*hexene at 140° in the presence of a small amount of sulphur gives poor yields of the thiol and monosulphide, with high recovery of hydrogen sulphide.

The predominantly disulphidic nature of the di*cyclo*hexyl polysulphide fraction is probably due to two factors : first, the insufficiency of sulphur, through its prior reaction

with the amine (higher polysulphides are formed only when high proportions of sulphur are available in the base-catalysed thiol oxidation); and secondly, the removal of the central sulphur atoms in the polysulphide by the amine as referred to above (p. 2082). The sulphur so removed becomes available for reaction with the amine according to (1) and for subsequent olefin sulphuration processes. The absence of any reaction between dialkyl disulphides and secondary amines at 140°, however, precludes the possibility of any di-*cyclo*hexyl monosulphide being formed by a sulphur-stripping process of the above type.

Undoubtedly olefin–sulphur interaction leading to alkyl alkenyl polysulphides (Farmer and Shipley, *loc. cit.*) competes initially with the amine–sulphur and ensuing addition reactions depicted above, and such competition may well be facilitated by amine catalysis since it is known that amines increase the rate of sulphur–rubber combination (*e.g.*, Williams, *Ind. Eng. Chem.*, 1947, **39**, 901). However, the exclusively saturated nature of the products indicates that the *cyclo*hexenyl *cyclo*hexyl polysulphide initially formed must undergo further additive sulphuration by means of (VI) and *cyclo*hexanethiol, and thus acts as the precursor of the observed saturated polymeric sulphides (4). The mono- and di-sulphidic nature of the sulphur linkages in the polymer is again due to the incursion of the amine–polysulphide desulphuration process described above :



. . (4)

It is believed that olefinic sulphuration processes of the above type would occur, with only minor modifications, were diethylamine to be substituted by most classes of aliphatic and aromatic amines since the latter readily liberate hydrogen sulphide on reaction with sulphur at elevated temperatures (Levesque, *loc. cit.*; Hodgson, *J.*, 1924, **125**, 1855; Johnson and Moore, *J. Amer. Chem. Soc.*, 1935, **57**, 1287; McMillan and King, *loc. cit.*; Brace, *ibid.*, 1953, **75**, 357). Only the combined absence of amino-hydrogen and methylene groups vicinal to the nitrogen atom prevents the formation of hydrogen sulphide (Johnson and Moore, *loc. cit.*). An example of this class of amine is dimethylaniline, and it is noteworthy that reaction of this amine with *cyclo*hexene and sulphur at 140° yielded alkyl alkenyl polysulphides comparable to those obtained from the *cyclo*hexene–sulphur reaction. This finding further supports the view that diethylamine–sulphur interaction according to (1) is an essential prior step to the subsequent additive sulphuration of the olefin by (VI) and *cyclo*hexanethiol.

Sulphuration of Olefins with NN′*-Thiobisamines.*—Bedford (*loc. cit.*) was the first to show that *NN*′-thiobisamines effectively vulcanise rubber, and this has since been confirmed by Blake (U.S.P. 2,325,735/1943), Hand (U.S.P. 2,490,518/1949), and Beaver and Throdahl (*Rubber Chem. Tech.*, 1944, **17**, 896; 1945, **18**, 110). More recently these compounds, particularly *NN*′-dithiobismorpholine, have come into prominence as vulcanising agents which impart reduced scorching and superior ageing characteristics to furnace-black stocks (Sibley, *ibid.*, 1951, **24**, 211; Throdahl and Harman, *Ind. Eng. Chem.*, 1951, **43**, 421). It is thus of importance to study the function of such compounds as olefinic sulphurating agents and the results of a preliminary study with *NN*′-thiobisdiethylamine (VII) are now described. Reaction of (VII) with *cyclo*hexene at 140° yielded di*cyclo*hexyl mono- and di-sulphides, diethylamine, and (IV), together with much unidentified material of high molecular weight. The reaction characteristics in this case thus closely resemble those of the diethylamine–sulphur–*cyclo*hexene system and it would seem that similar sulphurating mechanisms are operative. This conclusion is strengthened by the behaviour of (VII) on thermal decomposition at 140°, for diethylamine, (IV), (V), and (VI) were formed, the infra-red spectra of the reaction products being very similar to those from the diethylamine–sulphur reaction at 140°. Investigations are continuing of the olefinic-sulphuration capabilities and thermal decomposition characteristics of (VII) and related compounds.

Experimental

Infra-red spectra were recorded on a Grubb–Parsons single-beam spectrometer. Microanalyses were conducted under the supervision of Dr. W. T. Chambers.

Materials.—*cyclo*Hexene, freed from peroxide and distilled from sodium under nitrogen, had b. p. 82·5—82·6°/755 mm., n_D^{20} 1·4472 (Found: C, 87·8; H, 12·25. Calc. for C_6H_{10}: C, 87·7; H, 12·3%). Infra-red analysis showed the absence of carbonyl and hydroxyl groups. Sulphur was purified by Bacon and Fanelli's method (*Ind. Eng. Chem.*, 1942, **34**, 1043). Diethylamine, dried (KOH) and fractionated, had b. p. 55·0°/765 mm., n_D^{20} 1·3855. Infra-red analysis confirmed the absence of triethylamine.

Action of Piperidine on Sulphur and Alkyl Tetrasulphides at Room Temperature. (With Drs. G. H. Thomas and R. F. Naylor.)—A mixture of piperidine (10·0 g.) and sulphur (3·0 g.) in benzene (10 ml.) readily precipitated a dark orange complex on storage under nitrogen. Removal of the solvent and excess of piperidine by evaporative distillation *in vacuo* at room temperature yielded the *complex* as a dark orange, viscous oil (Found: C, 45·85; H, 7·5; N, 8·15. $C_{10}H_{22}N_2S_4,\frac{1}{2}C_6H_6$ requires C, 46·3; H, 7·4; N, 8·3%). Dilution of the complex, similarly derived from sulphur (3·2 g.) and piperidine (8·6 g.), with ethanol precipitated sulphur (3·1 g.), which on treatment with aqueous sodium sulphite rapidly dissolved to give sodium thiosulphate. Acidification of the ethanolic filtrate with ethanolic hydrogen chloride (15 g.; 40% solution) and evaporation *in vacuo* gave piperidine hydrochloride (9·7 g.), and extraction of the filtrate with water gave further sulphur (0·07 g.; total recovery 99%).

Di*iso*propyl tetrasulphide (6·4 g., 1 mol.), b. p. 67·5—70°/0·04 mm., n_D^{20} 1·5842 (Found: C, 33·55; H, 6·4; S, 60·15. Calc. for $C_6H_{14}S_4$: C, 33·6; H, 6·6; S, 59·8%), was mixed with piperidine (4 mol.) and kept at room temperature for 24 hr. under nitrogen. The dark brown product was taken up in ether and shaken successively with 40% aqueous sodium sulphite, water, 2N-hydrochloric acid, and aqueous sodium hydrogen carbonate. After drying ($MgSO_4$) and removal of the solvent, the product was distilled to give: (i) b. p. 56—59°/10 mm., n_D^{20} 1·4952 (1·52 g.) (Found: S, 43·65%), (ii) b. p. 60—65°/10 mm., n_D^{20} 1·5052 (1·29 g.) (Found: S, 46·5%), (iii) b. p. 45—60°/0·1 mm., n_D^{20} 1·5281 (1·47 g.) (Found: S, 51·35%), (iv) residue (0·19 g.) (Found: S, 51·9. Calc. for $C_6H_{14}S_2$: S, 42·7%. Calc. for $C_6H_{14}S_3$: S, 52·7%). Acidification of the sulphite extract gave sulphur (1·22 g.). The mild sulphite treatment used did not itself remove any of the combined sulphur of the tetrasulphide. Similar results were obtained with di-*n*-butyl, di-*tert.*-butyl, and dibenzyl tetrasulphides, the last giving ~70% of dibenzyl disulphide, m. p. 70—71° (Found: S, 26·0. Calc. for $C_{14}H_{14}S_2$: S, 26·0%). The ease of desulphuration of the tetrasulphides by piperidine followed the order: dibenzyl- > di-*n*-butyl- > di-*iso*propyl- > di-*tert.*-butyl-.

Attempted Low-temperature Sulphuration of cyclo*Hexene.*—A mixture of sulphur (5·0 g.), diethylamine (15 g.), and *cyclo*hexene (25 g.) was heated under nitrogen for 6 hr. at *ca.* 60°. Removal of excess of amine and olefin on the water-bath and addition of water to the residue gave unchanged sulphur (4·8 g.) and a liquid fraction which on distillation gave no sulphurated product. A similar reaction with piperidine at 55—60° for 4 hr. gave only a tar which slowly liberated sulphur with water. Use of di*cyclo*hexylamine at *ca.* 80° was likewise unsuccessful.

Reaction of Diethylamine and Sulphur at 140°.—A mixture of the amine (30 g.) and sulphur (10 g.) was heated at $<10^{-3}$ mm. in a Carius tube at 140° ± 1° with gentle shaking for 2½ hr. Diethylammonium hydrogen sulphide (9·3 g.) was filtered off under nitrogen from the liquid product, and after being washed with a little ice-cold ether and further purified by repeated vacuum-sublimation was identical with an authentic sample [m. p. and mixed m. p. (sealed-tube) 57—62°] (Achterhof, Conaway, and Boord, *J. Amer. Chem. Soc.*, 1931, **53**, 2682). No unreacted sulphur remained after the sublimation. The reddish-brown filtrate, after removal of unchanged amine, gave a product (15·4 g.), b. p. 62—68°/0·05 mm., shown by elementary and spectroscopic analysis to be mainly (IV) together with a little (V). When this material was heated with aqueous sodium hydroxide it gave ethylamine, and on refluxing for 1 hr. with 50% hydrochloric acid it gave hydrogen sulphide and acetic acid, the latter being identified by its *S*-benzylthiuronium salt, m. p. and mixed m. p. 136—137°. Raney nickel hydrogenolysis of the material gave diethylamine, identified as its toluene-*p*-sulphonyl derivative, m. p. and mixed m. p. 60°. Reaction with methyl iodide afforded a liquid methiodide which gave with alkali and subsequent fractionation N-*ethyl*-S-*methyl*iso*thioacetamide*, b. p. 44—48°/12 mm., n_D^{20} 1·4893 (Found: C, 51·55; H, 9·45; N, 11·9. $C_5H_{11}NS$ requires C, 51·3; H, 9·4; N, 11·9%). These reactions establish (IV) as a major component of the above material and this was confirmed by the close identity of its ultra-violet absorption spectrum with that of synthetic (IV).

A second experiment with the same quantities of amine and sulphur heated for 5 hr. at 140° ± 0·5° gave (VI), unreacted sulphur (6·6 g.), and the ligroin-insoluble material (5·1 g.) consisting of (IV) and (V), b. p. 66—67°/0·02 mm., n_D^{20} 1·5525 (Found: C, 49·5; H, 9·2; N, 12·4%).

Synthesis of N-Ethylthioacetamide (IV).—This compound, synthesised from ethylamine and either (*a*) thioacetamide or (*b*) *n*-propyl thionacetate, had b. p. 63—66°/0·02 mm., n_D^{20} 1·5590 (4·2 g.) (Found: C, 46·6; H, 8·9; N, 14·3. Calc. for C_4H_9NS: C, 46·6; H, 8·7; N, 13·6%). Light absorption: max., 2640, 3260 Å; ε, 1260, 5·4, respectively.

When (IV) was heated *in vacuo* at 140° ± 1° for 20 hr. it was recovered completely unchanged as revealed by elementary and infra-red analysis.

Reaction of Triethylamine and Sulphur at 140°.—Triethylamine (40 g.; b. p. 89·5°/759 mm.; n_D^{20} 1·4003) and sulphur (10 g.) were heated at <10^{-3} mm. in a Carius tube at 140° ± 1° for 21 hr. After removal of carbonaceous matter (3·9 g.) in nitrogen, the filtrate was evaporated on the steam-bath under reduced pressure. Distillation of the residue gave (V), b. p. 68—70°/0·5 mm. (17·5 g.); redistillation gave a colourless liquid, b. p. 63—64°/0·1 mm., n_D^{20} 1·5445 (Found: C, 54·2; H, 9·7; N, 10·5; S, 25·3. Calc. for $C_6H_{13}NS$: C, 54·9; H, 9·9; N, 10·7; S, 24·4%).

Synthesis of NN-*Diethylthioacetamide* (V).—(1) *NN*-Diethylacetamide [5·75 g.; b. p. 70—72°/10 mm.; n_D^{20} 1·4390 (Found: C, 62·75; H, 11·55; N, 12·4. Calc. for $C_6H_{13}ON$: C, 62·6; H, 11·3; N, 12·2%)] was refluxed with phosphorus pentasulphide (2·3 g.) in benzene (20 ml.) for 10 min., to give (V), b. p. 55°/0·07 mm., n_D^{20} 1·5298 (4·5 g.) (Found: C, 54·3; H, 9·9; N, 11·1; S, 22·7. Calc. for $C_6H_{13}NS$: C, 54·9; H, 9·9; N, 10·7; S, 24·7%), containing a little of the unchanged amide. Comparison of the infra-red spectrum of this material with that of the sulphur–triethylamine product revealed practical identity: in particular, strong bands at 1282, 1242, 1031, 928, and 839 cm.$^{-1}$ were present in both spectra, but absent from the spectrum of (IV).

(2) On heating a mixture of (IV) (4·0 g.) and diethylamine (5·0 g.) *in vacuo* at 140° ± 1° for 20 hr. and fractionation of the product, there were obtained two fractions: (i) b. p. 53—66°/0·1 mm., n_D^{20} 1·5552 (2·1 g.) (Found: C, 47·3; H, 8·75; N, 13·7%), and (ii) b. p. 66—68°/0·1 mm., n_D^{20} 1·5595 (1·6 g.) (Found: C, 46·9; H, 8·8; N, 13·3%). The infra-red spectra of (i) and (ii) were practically identical and indicated that both were mainly unchanged (IV). However, five bands at 1282, 1242, 1031, 928, and 839 cm.$^{-1}$ (referred to above) indicated the presence of a minor amount of (V).

Reaction of Diethylamine and Sulphur with cyclo*Hexene at* 140°.—(1) The amine (30 g.), sulphur (10 g.), and the olefin (50 g.) were heated *in vacuo* (<10^{-3} mm.) in a Carius tube at 140° ± 1° for 21 hr. with gentle rocking. The cooled product was filtered under nitrogen to remove (VI) (2·1 g.), and then freed from amine and olefin by evaporation under reduced pressure. Addition of excess of ligroin (b. p. 40—60°) precipitated an oil (i) (4·5 g.) and the main ligroin solution on extraction with 50% hydrochloric acid (3 × 25 ml.) gave an extract (ii). The ligroin solution was washed with aqueous sodium hydrogen carbonate, then water, and dried ($CaCl_2$). The absence of thiol in the solution was confirmed by a negative reaction with copper butyl phthalate. Removal of the solvent gave a main product (26·0 g.) which on fractionation

Fraction no.	B. p./mm.	Wt. (g.)	Found (%) C	H	N	S	C : H	n_D^{20}	*M* (ebull. in C_6H_6)
(iii)	~60°/0·02 mm.	4·35	71·4	11·0	0·27	17·4	6 : 11	1·5181	190
(iv)	75—78°/0·05 mm.	5·41	71·55	11·05	0·32	17·4	6 : 11·1	1·5185	—
(v)	78—82°/0·05 mm.	3·30	69·85	10·75	0·44	18·85	6 : 11	1·5235	201
(vi)	Short-path distn. at 120—140°	2·0	64·2	9·4	0·40	26·45	6 : 10·5	1·5610	—
(vii)		4·6	64·05	9·3	0·38	26·3	6 : 10·4	1·5622	303
(viii)		2·3	63·5	9·2	0·37	27·2	6 : 10·4	1·5693	350
	Calc. for $C_{12}H_{22}S$		72·7	11·1	0	16·2	6 : 11	—	198
	Calc. for $C_{12}H_{22}S_2$		62·6	9·55	0	27·8	6 : 11	—	230

in nitrogen gave fractions as shown in the Table. The final residue (ix) (2·20 g.) was dissolved in benzene and chromatographed on alumina. After elution with benzene, followed by ligroin containing 2% of ethanol, the solvent was removed from the eluate to give a clear, yellow glass which was dried at <10^{-3} mm. [Found: C, 61·9; H, 8·35; N, 0·33; S, 30·4%; *M* (ebullioscopic in benzene), 520].

Examination of the Fractions.—Fraction (i) on distillation gave a main fraction, a colourless liquid (4·1 g.), b. p. 67—68°/0·05 mm., n_D^{20} 1·5485 (Found: C, 53·5; H, 9·35; N, 9·9; S, 26·6%), shown by infra-red analysis to be mainly *N*-ethylthioacetamide (IV), together with minor amounts of (V) and *cyclo*hexyl sulphides. The acidic extract (ii) was made just alkaline at

0°, and the resultant oil taken up in chloroform, dried (Na_2SO_4), and distilled, to give a main fraction, b. p. 58—60°/0·02 mm. (4·1 g.), n_D^{20} 1·5490 (Found: C, 52·0; H, 9·25; N, 12·1; S, 25·7%), shown by infra-red analysis to be (IV), with a minor amount of (V). The infra-red spectra, elementary analysis, and molecular weights of fractions (iii)—(ix) indicated that the earlier fractions (iii)—(v) were entirely di*cyclo*hexyl mono- and di-sulphides, and the later fractions (vi)—(ix) were saturated polymeric *sulphides* (I); the absence of unsaturation due to *cyclo*hexenyl groups was definitely established. The ultra-violet absorption of the recovered olefin indicated only *ca.* 1% of benzene and negligible *cyclo*hexa-1 : 3-diene.

Hydrogenolysis of the Sulphurated Polymer.—The sulphurated polymeric fractions, typified by (vi)—(ix) above, from various experiments were combined and chromatographed on alumina as described for (ix) [Found: C, 64·2; H, 9·2; S, 26·0%; *M* (ebullioscopic in benzene), 315. Calc. for $C_{18}H_{32}S_3$: C, 62·8; H, 9·3; S, 27·9%; *M*, 344. Calc. for $C_{18}H_{32}S_2$: C, 69·2; H, 10·25; S, 20·5%; *M*, 312]. The polymer (8·0 g.) was slowly added to a stirred suspension of lithium aluminium hydride (4·0 g.) in tetrahydrofuran (100 ml.) and then refluxed for 3 hr. On decomposition with ice and 2N-sulphuric acid no hydrogen sulphide was evolved, indicating the complete absence of polysulphide groups. Working up of the product in the usual way gave a material which on fractionation yielded: (i) *cyclo*hexanethiol, b. p. ~74°/42 mm. (1·75 g.), n_D^{20} 1·4830 (Found: C, 62·4; H, 10·4; S, 26·4%; C : H, 6 : 12. Calc. for $C_6H_{12}S$: C, 62·1; H, 10·3; S, 27·65%), containing a trace of tetrahydrofuran [infra-red analysis confirmed the presence of both these compounds, and treatment of (i) with hot aqueous mercuric cyanide yielded the mercuric salt, m. p. and mixed m. p. with an authentic sample, 71°]; (ii) b. p. 90°/0·05 mm. (2·30 g.), n_D^{20} 1·5502 [Found: C, 62·5; H, 9·35; S, 26·65; SH, 15·6%; *M* (ebullioscopic in benzene), 214. Calc. for $C_{12}H_{22}S_2$: C, 62·6; H, 9·55; S, 27·8; SH, 14·3%; *M*, 230]; and (iii) distilled in a short-path still at 120—135° (3·1 g.), n_D^{20} 1·5530 [Found: C, 67·8; H, 9·8; S, 21·75%; *M* (ebullioscopic in benzene), 293. Calc. for $C_{18}H_{32}S_2$: C, 69·2; H, 10·25; S, 20·5%; *M*, 312]. Infra-red analysis of (ii) showed the complete absence of unsaturated groups and the spectrum resembled that of the original sulphide in many respects, except that a strong thiol band was now present due to the *thiol sulphide* (II). Similar examination of (iii) indicated that this fraction contained little thiol, but was otherwise generally similar to (ii). The spectrum was almost identical with that of the original sulphurated polymer and the combined analytical and spectroscopic data indicate (iii) to be mainly the di*cyclo*hexylthio*cyclo*hexane (III). The thiol content of (ii) is slightly higher than is consistent with pure (II) and this must be attributed to the presence of *cyclo*hexanethiol or, possibly, to traces of *cyclo*hexanedithiol, but positive evidence was lacking for the latter.

(2) Repetition of the sulphuration process as described under (1) above, except for a reaction time of 5 hr., gave the ligroin-insoluble oil and (VI), together with a main sulphide product (20·4 g.). The latter was extracted with 15% sulphurous acid, washed with water, dried, and fractionated to give: (i) b. p. 60—65°/0·04 mm. (3·8 g.), n_D^{20} 1·5400 (Found: C, 57·05; H, 9·9; N, 8·5; S, 22·6%); (ii) b. p. 65—95°/0·04 mm. (3·55 g.), n_D^{20} 1·5360 (Found: C, 62·85; H, 10·15; N, 4·5; S, 21·85%); (iii) b. p. 95—105°/0·04 mm. (1·35 g.), n_D^{20} 1·5488 (Found: C, 62·15; H, 9·35; N, 0·82; S, 27·3%); (iv) " molecular " distillate (1·60 g.), n_D^{20} 1·5740 (Found: C, 60·2; H, 8·7; N, 1·0; S, 30·2%); (v) " molecular " distillate (1·61 g.), n_D^{20} 1·5772 (Found: C, 59·8; H, 8·7; N, 0·75; S, 30·85%); and a residue (vi) (5·30 g.), chromatographed in the usual manner [Found: N, 1·5; S, 33·05%; *M* (ebullioscopic in benzene), 458]. Prolonged extraction of (i) and (ii) with sulphurous acid failed to remove the nitrogenous material, and the acidic extract on evaporation was free from thionate. Infra-red analysis of (i)—(v) again confirmed *cyclo*hexyl sulphides to be major constituents, *cyclo*hexenyl groups definitely being absent. Comparison of the spectra with those of authentic *NN'*-thiobisamines $(Et_2N)_2S_x$ indicated the absence of the latter, the nitrogenous component being characterised as a mixture of the thioamides (IV) and (V).

Independent experiments showed (*a*) that treatment of *NN'*-monothiobisdiethylamine (VII) with 15% sulphurous acid readily gave the corresponding trithionate as white needles, m. p. 151°, from ethanol (cf. Lecher *et al.*, *loc. cit.*), and (*b*) that repeated extraction of an authentic mixture of (VII) and di*cyclo*hexyl monosulphide with 15% sulphurous acid effected complete separation of the two components, the former being obtained as the corresponding water-soluble trithionate in 90—95% yield.

Reaction of Diethylammonium Hydrogen Sulphide (VI) *with* cyclo*Hexene at* 140°.—Diethylamine (50 ml.), *cyclo*hexene (50 ml.), and sulphur (0·4 g.) were heated with hydrogen sulphide (~4·5 g.) in a nitrogen-filled Carius tube for 22 hr. at 140°. After removal of (VI) (4·2 g.) by filtration, fractionation gave (i) unchanged amine and olefin, b. p. 40—80°/760 mm., (ii) b. p.

60—80°/25 mm. (0·8 g.), n_D^{20} 1·4890 (Found: C, 67·15; H, 10·8; N, 0·43; S, 23·0%), (iii) b. p. 64—84°/0·1 mm. (2·2 g.), n_D^{20} 1·5272 (Found: C, 64·2; H, 10·45; N, 3·5; S, 20·9%). Infra-red analysis indicated that (ii) was mainly *cyclo*hexanethiol and (iii) a mixture of di*cyclo*hexyl sulphides and (V).

Reaction of Dimethylaniline and Sulphur at 140°.—When the amine (30 ml.) and sulphur (6·4 g.) were heated under reflux in nitrogen for 5 hr. at 140°, then cooled and filtered, the majority (5·8 g.) of the sulphur was recovered and the filtrate yielded only unchanged amine.

Reaction of Dimethylaniline and Sulphur with cyclo*Hexene*.—The amine (30 ml.), sulphur (5·0 g.), and olefin (25·0 g.) were heated in pure nitrogen for 5 hr. at 140°. Recovered sulphur (1·48 g.) was isolated on taking up the product in ice-cold ligroin. The filtrate was freed from solvent, and the residue fractionated to give: (i) recovered amine, b. p. 74—75°/11 mm. (35 g., 28·0 ml.), n_D^{20} 1·5587 (Found: C, 79·2; H, 9·05. Calc. for $C_8H_{11}N$: C, 79·3; H, 9·1%), and (ii) a dark viscous residue which was dissolved in benzene, extracted with 50% hydrochloric acid, washed with water, dried, and chromatographed on alumina to yield, after removal of the solvent, a polysulphide (4·8 g.) containing traces of unreacted sulphur (Found: C, 34·5; H, 4·55; N, 0·13%; C : H, 6 : 9·5). Infra-red analysis of this material revealed the presence of *cyclo*hexenyl groups, the spectrum closely resembling that of the polysulphide obtained from reaction of sulphur and *cyclo*hexene at 140°, and being different from those of the *cyclo*hexyl sulphides obtained from the diethylamine–sulphur–*cyclo*hexene reaction described above.

Synthesis of NN′*-Mono- and -Poly-thiobisdiethylamines*.—(1) The compound (VII), prepared according to Blake (*J. Amer. Chem. Soc.*, **1943, 65, 1267**), was obtained as a faintly yellow liquid, b. p. 78°/10 mm., n_D^{20} 1·4622 (73%) (Found: N, 15·9; S, 18·35. Calc. for $C_8H_{20}N_2S$: N, 15·9; S, 18·2%).

(2) The *NN′*-dithiobisamine, obtained from diethylamine and sulphur monochloride (purified by repeated distillation over sulphur under reduced pressure) according to Throdahl and Harman (*loc. cit.*), had b. p. 74·5°/0·05 mm., n_D^{20} 1·5132 (Found: N, 13·0; S, 30·6, 30·8. Calc. for $C_8H_{20}N_2S_2$: N, 13·4; S, 30·8%).

(3) The *NN′*-trithiobisamine (cf. Levi, *Gazzetta*, **1931, 61**, 286) was obtained as a light yellow liquid, b. p. 101·5—103·5°/0·3 mm., n_D^{22} 1·5428 (Found: N, 11·5; S, 39·3. Calc. for $C_8H_{20}N_2S_3$: N, 11·6; S, 40·0%). Infra-red analysis confirmed the absence of the above *NN′*-thioamines from the sulphur–amine–*cyclo*hexene reaction product.

Thermal Decomposition of NN′*-Monothiobisdiethylamine* (VII).—This compound (2·40 g.) was heated *in vacuo* at 140° ± 1° for 21 hr. The resulting dark brown liquid was distilled at 50 mm., and the distillate collected in a trap cooled in liquid air. The distillate contained diethylamine, characterised as its toluene-*p*-sulphonate, m. p. and mixed m. p. 58—59°. During the distillation diethylammonium hydrogen sulphide (VI) collected in the condenser. The residual liquid (1·50 g.) on distillation gave a main fraction, b. p. 50—54°/0·1 mm., n_D^{20} 1·5515 (Found: N, 12·3; S, 27·55%), shown by infra-red analysis to be mainly (IV), but additional bands at 839, 928, 1031, 1242, and 1282 cm.$^{-1}$ indicated a minor amount of (V). The formation of (IV) was further confirmed by the chemical methods described on p. 2085. An undistillable tar (0·80 g.) which remained from the above distillation was not further examined.

Reaction of (VII) *with* cyclo*Hexene*.—The compound (VII) (17·6 g., 0·1 mole) and the olefin (41·0 g., 0·5 mole) were heated *in vacuo* for 21 hr. at 140° ± 1°. Treatment of the product with ligroin, followed by filtration, afforded an insoluble tar together with crystalline (VI) from the main soluble material. The latter, after removal of volatile material, gave a product (11·5 g.) which on distillation gave: (i) b. p. ~70°/0·05 mm., n_D^{20} 1·5330 (1·0 g.) (Found: C, 59·8; H, 9·85; N, 8·25; S, 20·35%); (ii) b. p. 70—80°/0·05 mm., n_D^{20} 1·5352 (1·1 g.) (Found: C, 59·4; H, 9·9; N, 7·45; S, 22·3%); (iii) b. p. 80—85°/0·05 mm., n_D^{20} 1·5332 (0·6 g.) (Found: C, 65·1; H, 10·05; N, 5·05; S, 19·3%). Extensive decomposition set in at this stage and no further attempt was made to fractionate the residual tar (Found: N, 3·45; S, 27·3%). The infra-red spectra of (i)—(iii) were similar and showed the presence of di*cyclo*hexyl sulphides and (IV), and the absence of *cyclo*hexenyl groups and (VII).

In a second experiment, (VII) (10·0 g.) and *cyclo*hexene (20·0 g.) were heated for 16 hr. at 140° ± 1°. After separation of tar (1·0 g.), the liquid product was distilled at 20°/12 mm., and the distillate collected in a trap cooled in liquid air. Water was added to the distillate, and the mixture titrated with standard hydrochloric acid to estimate the diethylamine (Found: 5·29 g.). The *cyclo*hexene layer of this distillate was separated, washed, dried, and distilled to give the olefin, b. p. 82°/760 mm., n_D^{20} 1·4468, without a residue, thus confirming that the basic material was diethylamine and not unchanged (VII).

Reactions of N*-Ethylthioacetamide* (IV).—(1) *Action on* cyclo*hexene*. The olefin (5·0 g.) and

(IV) (3·15 g.), b. p. 70—72°/0·1 mm., n_D^{20} 1·5600, were heated *in vacuo* for 20 hr. at 140° ± 1°. The product consisted of unchanged olefin and a separate layer, b. p. 50—52°/0·02 mm., n_D^{20} 1·5601 (2·90 g.), which was shown by infra-red analysis to be unchanged (IV).

(2) *Separation from* cyclo*hexyl sulphides.* A mixture of *cyclo*hexyl sulphides and (IV), b. p. 96—100°/2 mm. (Found: N, 6·4%), was dissolved in ligroin (40 ml.) and extracted with cold 50% hydrochloric acid (2 × 30 ml.). The ligroin layer yielded on distillation a fraction, b. p. 93—97°/1 mm. (Found: N, 0·17%), the infra-red spectrum of which showed the absence of (IV).

(3) *Catalysis of thiol oxidation by sulphur.* Ethanethiol (8·4 g.) was mixed with sulphur (4·3 g.) and (IV) (0·1 g.) at room temperature. After a short induction period, hydrogen sulphide was evolved, and the product on fractionation gave a mixture of diethyl di- and poly-sulphides.

Non-reaction of Diethylamine with cyclo*Hexene.*—A mixture of the amine (3·0 g.) and olefin (5·0 g.) was heated *in vacuo* for 21 hr. at 140° ± 1°. On distillation of the product only unchanged reactants, b. p. 56—82°/760 mm. (7·2 g.), were isolated.

*Non-reaction of Di*cyclo*hexylamine with Dimethyl Disulphide at* 140°.—The amine (4·5 g., 0·025 mole) and the disulphide (2·35 g.; 0·025 mole; n_D^{20} 1·5200) were heated in pure nitrogen for 5 hr. at 140° ± 1°. Fractionation of the product gave unchanged disulphide, b. p. 104—108°/760 mm., n_D^{20} 1·5208, and amine, b. p. 118—120°/10 mm., n_D^{20} 1·4875. No dimethyl monosulphide was detectable.

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The Reactions of Amines and Sulphur with Olefins. Part II. The Reaction of Diethylamine and Sulphur with Trialkylethylenes.*

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The reaction of diethylamine and sulphur with trialkylethylenes, R·CMe:CHR′, at 140° yields *tert.*-alkanethiols and di-*tert.*-alkyl disulphides as major products, with only minor amounts of the corresponding polysulphides and sulphurated polymers containing three or more olefin units linked by sulphur bridges. The degree of sulphuration is much lower than with the corresponding *s*-dialkylethylene, *cyclo*hexene (Part I), and monosulphide formation is negligible, both observations indicating that steric influences govern the nature and yield of the sulphurated products.

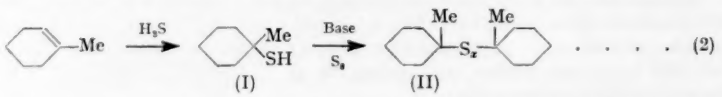
THE use of the diethylamine–sulphur combination for the sulphuration of *cyclo*hexene at 140° (Part I *) has been extended to the trialkylethylenes, R·CMe:CHR′, which are used as the simplest analogues of rubber hydrocarbon. The reaction characteristics observed with *cyclo*hexene indicated that a major sulphurating agent was hydrogen sulphide, formed by prior interaction of the amine and sulphur, and it was argued that trialkylethylenes would react first to give the intermediate *tert.*-alkanethiol, R·CMe(SH)·CH_2R′, by polar addition of hydrogen sulphide, which would combine with a second olefin molecule to give a di-*tert.*-alkyl monosulphide:

$$\text{R·CMe:CHR}' \xrightarrow{H_2S} \text{R·CMe(SH)·CH}_2\text{R}' \xrightarrow{\text{Olefin}} \text{S(CMeR·CH}_2\text{R}')_2 \quad . \quad . \quad . \quad . \quad (1)$$

Examination of the reaction of diethylamine and sulphur with 1-methyl*cyclo*hexene at 140° established the polar nature of the sulphuration process, but also revealed significant differences from the analogous reaction with *cyclo*hexene and the reactions

* Part I, preceding paper.

represented by (I) above, *viz.*, (i) a considerably lower yield of sulphurated product comprising 1-methyl*cyclo*hexane-1-thiol (I), a major amount of di-(1-methyl*cyclo*hexyl) disulphide (II; $x = 2$), and a minor amount of the sulphurated polymer typical of that formed in the *cyclo*hexene reaction (Part I); (ii) the absence of di-(1-methyl*cyclo*hexyl) monosulphide (II; $x = 1$); and (iii) the isolation of a considerable amount of diethylammonium hydrogen sulphide, consistent with (i) above. It is noteworthy, however, that the degree of sulphuration effected under the present conditions is much greater than that obtained by Naylor (*J.*, **1947**, 1532) by the sulphur-catalysed normal addition of hydrogen sulphide to trialkylethylenes under comparable or even more severe reaction conditions. The structures of the thiol and disulphide as (I) and (II; $x = 2$), respectively, were established by comparison of their chemical properties and infra-red spectra with those of (I) and 2-methyl*cyclo*hexane-1-thiol (III), and their derived polysulphides synthesised by unambiguous means. Such comparison substantiates the polar nature of the sulphuration process which must be represented as occurring mainly by reaction (2):



(I) (II) . . . . . (2)

The thiol (I) was synthesised by reductive cleavage of benzyl 1-methyl*cyclo*hexyl sulphide (IV) with sodium and liquid ammonia, (IV) being obtained by normal addition of toluene-ω-thiol to 1-methyl*cyclo*hexene in the presence of 75% (w/w) sulphuric acid. Attempted cleavage of (IV) with aluminium bromide (Harnish and Tarbell, *J. Amer. Chem. Soc.*, 1948, **70**, 4123) was unsuccessful, the only products isolated being 1-methyl-1-phenyl*cyclo*hexane and diphenylmethane; the former hydrocarbon apparently arose from attack of the intermediate 1-methyl*cyclo*hexyl carbonium ion on benzene which was used as solvent (cf. Dougherty and Lee, *J. Org. Chem.*, 1939, **4**, 48), and the latter by Friedel–Crafts arylation of the solvent by benzyl bromide. The thiol (III) was synthesised from α-(2-methyl*cyclo*hexyl)thiolacetate by Cunneen's method (*J.*, 1947, 138). The corresponding di- and poly-sulphides of (I) and (III) were obtained by base-catalysed sulphur oxidation of the thiols (Bloomfield, *J. Soc. Chem. Ind.*, 1948, **67**, 14).

(III) (IV)

The overall lower yield of sulphurated product as compared with the *cyclo*hexene reaction (Part I), the isolation of the thiol (I), and the absence of monosulphuide (II; $x = 1$) in the present reaction collectively suggest that the presence of trialkylethylene unsaturation in the olefin introduces some structural feature, probably steric, which impairs the additive capabilities of hydrogen sulphide and the derived *tert.*-thiol (I). The existence of such steric factors is indicated by examination of molecular models of (I) and (II; $x = 1$ and 2) and has been independently confirmed by determining the relative facilities with which (I) and (III) add both normally and abnormally to *cyclo*hexene and 1-methyl*cyclo*hexene.

Although the *tert.*-thiol (I) resists further addition to the parent olefin, its ability to undergo base-catalysed oxidation by sulphur to give the disulphide (II; $x = 2$) remains unimpaired, and thus the isolation of (I) in the present reaction must be attributed to the absence of sulphur, necessary for such thiol oxidation, in the later stages of the sulphuration process through its prior reaction with diethylamine (Part I).

It is clearly of importance to determine if the undesirable inhibition of the hydrogen sulphide and thiol additions to the parent olefin is specific to the trialkylethylene structure in 1-methyl*cyclo*hexene or is general to both cyclic and acyclic olefins of this type. This has been examined by studying the reaction of the diethylamine–sulphur combination with 2-methylpent-2-ene at 140°. In this case such inhibition was much less since a considerably larger yield of disulphide (VI; $x = 2$) was obtained, with little of the monosulphide (VI; $x = 1$) and polysulphide (VI; $x > 2$). A low yield was also obtained of a

saturated thiol, C_6H_{13}·SH, shown to be (V) by comparison of its chemical properties and infra-red spectrum with those of 2-methylpentane-2-thiol synthesised from the corresponding benzylthio-compound. The reaction course (3) thus closely resembles that followed by 1-methyl*cyclo*hexene:

$$CH_2Me{\cdot}CH{:}CMe_2 \xrightarrow[H_2S]{} CH_2Me{\cdot}CH_2{\cdot}CMe_2{\cdot}SH \xrightarrow[S_x\text{–base}]{\text{Olefin, } x=1} (CH_2Me{\cdot}CH_2{\cdot}CMe_2)_2S_x \quad . \quad (3)$$

(V) (x mainly 2) (VI)

The *tert.*-alkyl nature of the thiol (V) and the disulphide (VI; $x = 2$) again strongly supports the proposed polar course of the reaction.

Abortive attempts were made to effect sulphuration of trialkylethylenes either by means of the diethylamine–sulphur combination at 100° or by treating the olefin at room temperature with the active sulphur liberated from this combination by means of ethanol.

Experimental

Infra-red spectra were recorded on a Grubb–Parsons single-beam spectrometer. Microanalyses were conducted under the supervision of Dr. W. T. Chambers.

Preparation of Olefins.—1-Methyl*cyclo*hexene, prepared by iodine-catalysed dehydration of 1-methyl*cyclo*hexan-1-ol, had b. p. 109—109·8°/762 mm., n_D^{20} 1·4508 (Found: C, 87·35; H, 12·45. Calc. for C_7H_{12}: C, 87·4; H, 12·6%). Infra-red analysis indicated the absence of methylene*cyclo*hexane and ketonic and hydroxyl groups. 2-Methylpent-2-ene, similarly prepared from 2-methylpentan-2-ol, had b. p. 66·4—66·7°/760 mm., n_D^{20} 1·4005 (Found: C, 85·4; H, 14·35. Calc. for C_6H_{12}: C, 85·7; H, 14·3%). Infra-red analysis indicated that *ca.* 3% of vinylidene unsaturation, $CH_2{:}CR_2$, was present.

Synthesis of Reference Compounds for the 1-*Methyl*cyclo*hexene Reaction.*—(1) *Benzyl* 1-*methyl*-cyclo*hexyl sulphide* (IV). 1-Methyl*cyclo*hexene (96 g., 1 mole) was added dropwise with stirring to 75% (w/w) sulphuric acid (500 g.) at 0—5°. Toluene-ω-thiol (62 g., 0·5 mole) was then added, with continued stirring, during 1 hr. at 0—5° and then during 2 hr. at room temperature. The product was decomposed with ice and extracted with ether, and the extract washed successively with water, alkali, and water, dried (K_2CO_3), and distilled. The main distillate, b. p. 83—93°/0·3 mm., n_D^{20} 1·5470 (106 g.), on repeated fractionation, gave the pure *sulphide* (IV), b. p. 100—101°/0·1 mm., n_D^{20} 1·5538 (76·0 g.) (Found: C, 76·4; H, 9·25; S, 14·5. $C_{14}H_{20}S$ requires C, 76·4; H, 9·1; S, 14·5%). Use of 75% (v/v) sulphuric acid in the above reaction gave little of the desired sulphide (IV), the major products being dibenzyl disulphide (58·0 g.), m. p. 69—70° (Found: C, 68·45; H, 6·0; S, 25·55. Calc. for $C_{14}H_{14}S_2$: C, 68·3; H, 5·7; S, 26·0%), and a fraction (34·0 g.), b. p. 53°/0·05 mm., n_D^{20} 1·4950, containing a polymer of 1-methyl-*cyclo*hexene [Found: C, 87·15; H, 12·25; S, 0·4. Calc. for $(C_7H_{12})_n$: C, 87·4; H, 12·6%].

(2) 1-*Methyl*cyclo*hexane*-1-*thiol* (I). (*a*) The sulphide (IV) (22·0 g., 0·1 mole), suspended in liquid ammonia (400 ml.), was treated with small portions of sodium (5·5 g., 0·23 g.-atom) with rapid stirring until the solution became permanently blue. Ammonium chloride (14 g.) was then added, and the ammonia allowed to evaporate overnight, the last traces being removed on the water-pump. The product was made just acid with ice-cold 2N-hydrochloric acid and extracted with ether, and the extract fractionated, to give the *thiol* (I), b. p. 48°/11 mm., n_D^{20} 1·4853 (9·2 g.) (Found: C, 66·3; H, 10·7; S, 22·85. $C_7H_{14}S$ requires C, 64·6; H, 10·8; S, 24·6%), containing, as revealed by infra-red analysis, a trace of toluene not removed by further fractionation. Treatment of a neutral solution of the sodium salt of (I) with chloro-2 : 4-dinitrobenzene gave 2 : 4-*dinitrophenyl* 1-*methyl*cyclo*hexyl sulphide* as yellow flakes, m. p. 59—59·5°, from ethanol (Found: C, 52·65; H, 5·45; N, 9·8. $C_{13}H_{16}O_4N_2S$ requires C, 52·7; H, 5·4; N, 9·5%). Hot aqueous mercuric cyanide with (I) gave the *mercuric* derivative as feathery needles (from ethanol), m. p. 106—107° (Found: Hg, 43·4. $C_{14}H_{26}S_2Hg$ requires Hg, 43·7%).

(*b*) Treatment of the sulphide (IV) (11·0 g., 0·05 mole) during 2 days at room temperature with a solution of aluminium bromide (15·0 g., 0·056 mole) in benzene (100 ml.) and fractionation of the product gave only two hydrocarbon fractions: (i) b. p. 56—60°/0·05 mm., n_D^{20} 1·5462 (4·5 g.) (Found: C, 90·8; H, 9·2. Calc. for $C_{13}H_{18}$: C, 92·9; H, 7·1%. Calc. for $C_{13}H_{18}$: C, 89·6; H, 10·4%), and (ii) b. p. 60°/0·05 mm., n_D^{20} 1·5610 (4·7 g.) (Found: C, 91·4; H, 7·95%).

(3) *Di*-(1-*methyl*cyclo*hexyl*) *polysulphide* (II; $x = 3$—4). When the thiol (I) (5·2 g.) was mixed with sulphur (0·64 g.) and diethylamine (0·1 g.) at room temperature hydrogen sulphide was slowly evolved. Fractionation gave: (i) unchanged (I), b. p. 52°/15 mm., n_D^{20} 1·4879

(2·60 g.), and (ii) the polysulphide (II; $x = 3$—4), " molecularly " distilled as a yellow liquid, n_D^{20} 1·5810 (1·90 g.) (Found: C, 54·6; H, 8·35; S, 36·4. Calc. for $C_{14}H_{26}S_2$: C, 57·9; H, 8·97; S, 33·1. Calc. for $C_{14}H_{26}S_4$: C, 52·2; H, 8·1; S, 39·7%).

(4) 2-*Methyl*cyclo*hexane*-1-*thiol* (III). This compound, prepared according to Cunneen's method (*loc. cit.*), had b. p. 54—56°/10 mm., n_D^{20} 1·4950 (68%) (Found: C, 64·4; H, 10·7; S, 24·5. Calc. for $C_7H_{14}S$: C, 64·6; H, 10·8; S, 24·6%). It gave 2 : 4-*dinitrophenyl* 2-*methyl*-cyclo*hexyl sulphide* as yellow prisms (from ethanol), m. p. 87—88° (Found: C, 52·65; H, 5·35; N, 9·5. $C_{13}H_{16}O_4N_2S$ requires C, 52·7; H, 5·4; N, 9·5%). Oxidation of (III) (5·2 g.) with sulphur (0·64 g.) in the presence of diethylamine (0·1 g.) or *N*-ethylthioacetamide (0·1 g.) at room temperature gave hydrogen sulphide and a product which on fractionation yielded: (i) unchanged thiol, b. p. 55—56°/10 mm., n_D^{20} 1·4932 (2·52 g.); and (ii) a " molecular " distillate, n_D^{20} 1·5852 (2·1 g.), of mixed di-(2-methyl*cyclo*hexyl) polysulphides (Found: C, 53·5; H, 8·4; S, 38·6. Calc. for $C_{14}H_{26}S_4$: C, 52·2; H, 8·1; S, 39·7%).

(5) *Di-*(2-*methyl*cyclo*hexyl*) *monosulphide*. The thiol (III) (4·0 g., 1 mol.), 1-methyl*cyclo*-hexene (3·25 g., 1·1 mol.), and acetone (0·5 g.) were sealed *in vacuo* in a Pyrex tube, and irradiated with ultra-violet light for 16 hr. with water-cooling. Fractionation of the product gave: (i) unchanged thiol (III), b. p. 64—66°/20 mm., n_D^{20} 1·4940 (2·3 g.); and (ii) almost pure *monosulphide*, b. p. 62—64°/0·05 mm., n_D^{20} 1·5120 (1·80 g.) (Found: C, 73·9; H, 11·4; S, 14·25. $C_{14}H_{26}S$ requires C, 74·3; H, 11·5; S, 14·2%). Acid potassium permanganate oxidation of the monosulphide gave the corresponding *sulphone* as colourless prisms, m. p. 111—113°, from ethanol (Found: C, 64·9; H, 10·1; S, 12·25. $C_{14}H_{26}O_2S$ requires C, 65·1; H, 10·1; S, 12·4%).

Normal and Abnormal Additions of Thiols to Olefins.—(1) *Polar addition of* (I) *to* 1-*methyl*-cyclo*hexene*. The olefin (9·6 g.) was added slowly to sulphuric acid (50 g., 75% w/w) at 0—5° with vigorous stirring; the thiol (I) (6·5 g.) was then added, and stirring continued at room temperature for a further 15 min. Fractionation of the product gave: (i) a mixture (5·2 g.) of unchanged thiol (I) and olefin, b. p. 45—53°/12 mm., n_D^{20} 1·4670; and (ii) b. p. 58—67°/0·05 mm., n_D^{20} 1·5130 (6·1 g.) (Found: C, 77·85; H, 12·0; S, 10·35. Calc. for $C_{14}H_{26}S$: C, 74·3; H, 11·5; S, 14·2%), shown by infra-red analysis to be a mixture of di-(1-methyl*cyclo*hexyl) monosulphide and 1-methyl*cyclo*hexene polymer.

(2) *Abnormal addition of* (I) *to* 1-*methyl*cyclo*hexene*. Irradiation of a mixture of (I), the olefin, and acetone with ultra-violet light for 17 hr. at 15° gave no sulphide, the product being a mixture of unchanged reactants, as confirmed by infra-red analysis. Similar abnormal addition of *tert.*-butanethiol to 1-methyl*cyclo*hexene gave a sulphide yield of only 8—9% after 17 hours' irradiation at 15°.

(3) *Abnormal addition of* (I) *to* cyclo*hexene*. The thiol (I) (4·0 g., 1 mol.), the olefin (2·77 g., 1·1 mol.), and acetone (0·5 g.), irradiated as in (2) above, gave unchanged thiol (I) (2·50 g.), and slightly impure cyclo*hexyl* 1-*methyl*cyclo*hexyl sulphide* (1·70 g.), b. p. 66°/0·05 mm., n_D^{25} 1·5110 (Found: C, 74·1; H, 11·6; S, 14·5. $C_{13}H_{24}S$ requires C, 73·6; H, 11·3; S, 15·1%).

Reaction of Diethylamine and Sulphur with 1-*Methyl*cyclo*hexene at* 140°.—The amine (30·0 g.), sulphur (10·0 g.), and the olefin (40·0 g.) were heated *in vacuo* for 24 hr. at 140° ± 1°. Diethyl-ammonium hydrogen sulphide (8·5 g.) and a small amount of tar were separated from the product by filtration, and the filtrate was freed from unchanged amine and olefin by evaporation on the steam-bath under nitrogen. The residue was taken up in ligroin and extracted with 10% sodium hydroxide solution (3 × 25 ml.). The alkaline extract was acidified (hydrochloric acid) and extracted with ether, and the extract dried (Na_2SO_4) and fractionated to give: (i) b. p. 54—106°/12 mm., n_D^{20} 1·5090 (0·5 g.) (Found: C, 60·2; H, 9·5; N, 0·56; S, 28·1%); (ii) b. p. 106—110°/12 mm., n_D^{20} 1·5448 (1·1 g.) (Found: C, 51·65; H, 8·65; N, 3·3; S, 35·05%); and (iii) b. p. 46°/0·1 mm., n_D^{20} 1·5594 (1·1 g.) (Found: C, 47·9; H, 8·8; N, 11·5; S, 30·15. Calc. for C_4H_9NS: C, 46·4; H, 8·7; N, 13·6; S, 31·1%). Fractions (i) and (ii) contained the thiol (I), identified (m. p.s and mixed m. p.s) by its 2 : 4-dinitrophenyl sulphide derivative and its mercuric derivative. Infra-red analysis of (i) and (ii) confirmed that (I) was a major constituent, the isomeric thiol (III) being definitely absent; di-(1-methyl*cyclo*hexyl) sulphides (II) were present in minor amount. Infra-red analysis of (iii) indicated that it was nearly pure *N*-ethylthioacetamide, the thiol form of which presumably accounts for its solubility in aqueous alkali.

The ligroin fraction was washed with 50% hydrochloric acid (5 × 20 ml.) to remove remaining thioamides, and then with aqueous bicarbonate and water. Fractionation of the product gave: (iv) unchanged olefin (14·2 g.) containing a trace of (I), b. p. 50°/30 mm., n_D^{20} 1·4512 (Found: S, 1·6%); (v) pure (I) (1·90 g.), b. p. 50—51°/12 mm., n_D^{20} 1·4880 (Found:

C, 64·8; H, 10·75; N, 0·02; S, 24·3. Calc. for $C_7H_{14}S$: C, 64·6; H, 10·8; S, 24·6%), identified (m. p.s and mixed m. p.s) by its 2 : 4-dinitrophenyl sulphide and mercuric derivatives and by comparison of its infra-red spectrum with that of synthetic (I) and (III); and (vi) b. p. 56—85°/0·07 mm., n_D^{20} 1·5310 (3·6 g.) (Found: C, 62·9; H, 9·75; N, 1·6; S, 25·45. Calc. for $C_{14}H_{26}S_2$: C, 65·1; H, 10·1; S, 24·8%). Infra-red analysis of (vi) showed that it was mainly the disulphide (II; $x = 2$) with minor amounts of higher polysulphides (II; $x > 2$) and indicated the absence of thiols (I) and (III), di-(2-methyl*cyclo*hexyl) polysulphides, *N*-ethylthioacetamide, and all types of C:C unsaturation; weak bands were also present due to a minor amount of *NN*-diethylthioacetamide. The reddish-brown viscous residue (6·85 g.) on molecular distillation gave: (vii) n_D^{20} 1·5602 (Found: C, 63·6; H, 9·25; N, 1·35; S, 25·35%); (viii) n_D^{20} 1·5718 (Found: C, 62·4; H, 8·65; N, 1·2; S, 27·3%); and (ix) a residue which on chromatography on alumina yielded a clear yellow glass (Found: C, 60·65; H, 8·4; N, 0·55; S, 30·15%). Fractions (vii)—(ix) were mixtures of polysulphides (II; $x = 2$—3) together with polymeric material typical of that observed in the *cyclo*hexene reaction (Part I).

Synthesis of Reference Compounds for the 2-Methylpent-2-ene Reaction.—(1) *Benzyl* 1 : 1-*dimethylbutyl sulphide*, prepared (yield 90%) by a method analogous to that used for the synthesis of (IV), had b. p. 84—88°/0·5 mm., n_D^{20} 1·5230 (Found: C, 74·8; H, 9·5. $C_{13}H_{20}S$ requires C, 75·0; H, 9·6%).

(2) *2-Methylpentane-2-thiol* (V). (i) Reduction of the above sulphide (18·0 g.) with sodium in liquid ammonia, as described above for the synthesis of (II), yielded the slightly impure *thiol* (V) (71%), b. p. 36—38°/12 mm., n_D^{25} 1·4412 (Found: C, 62·35; H, 12·1; S, 25·75. Calc. for $C_6H_{14}S$: C, 61·0; H, 11·9; S, 27·1%). Infra-red analysis showed that the impurity was toluene. The thiol (V) gave a *mercuric* derivative as colourless needles, m. p. 75—76° (Found: S, 14·7; Hg, 46·9. $C_{12}H_{26}S_2Hg$ requires S, 14·7; Hg, 46·2%), from ethanol. Attempts to prepare the 2 : 4-dinitrophenyl sulphide derivative gave only 2 : 4-dinitrophenetole, m. p. 85°. Rheinboldt's test (*Ber.*, 1926, **59**, 1131) confirmed that (V) was a *tert.*-thiol.

(ii) Resublimed aluminium bromide (2·0 g.), in carbon disulphide (50 ml.), was treated with dry hydrogen sulphide at room temperature with the simultaneous addition of 2-methylpent-2-ene (16·8 g.). Hydrogen sulphide addition was continued for a further 15 min., and the mixture decomposed with ice and dilute hydrochloric acid and worked up in the usual way, to give the thiol (V) (6·8 g.), b. p. 36—37°/11 mm., n_D^{20} 1·4430 (Found: C, 59·2; H, 11·65; S, 25·55%). The infra-red spectrum was very similar to that of the thiol obtained in (i) above, though additional bands were present, due to some unidentified impurity. The thiol gave a mercuric derivative, m. p. and mixed m. p. with that from (i) 75—76°.

(3) *Di-*(1 : 1-*dimethylbutyl*) *polysulphide* (VI). The thiol (V) (4·72 g.) and sulphur (0·64 g.) on treatment with diethylamine (0·1 g.) during 10 hr. at room temperature gave unchanged (V) (2·4 g.), b. p. 40°/15 mm., and the polysulphide (VI; $x \sim 4$) obtained by molecular distillation as a pale yellow liquid (1·75 g.), n_D^{25} 1·5460 (Found: C, 49·4; H, 9·05; S, 41·7. Calc. for $C_{12}H_{26}S_4$: C, 48·3; H, 8·7; S, 42·9%).

Reaction of Diethylamine and Sulphur with 2-Methylpent-2-ene at 140°.—The amine (30·0 g.), sulphur (10·0 g.), and olefin (50·0 g.) were heated *in vacuo* at 140° ± 1° for 21 hr. with gentle rocking. After removal of diethylammonium hydrogen sulphide (0·6 g.), the product was treated with ligroin (b. p. 40—60°) and a tar (1·1 g.) separated. The ligroin solution was evaporated on the water-bath under nitrogen to remove unchanged amine and olefin, diluted with more ligroin, and extracted with cold 50% hydrochloric acid (4 × 25 ml.) to remove thioamides. The resultant ligroin fraction on distillation gave: (i) b. p. 45—50°/12 mm., n_D^{20} 1·4448 (2·3 g.), containing about 79% of the thiol (V) and a little monosulphide (VI; $x = 1$) (Found: C, 61·7; H, 11·95; N, 0·1; S, 26·3; SH, by copper butyl phthalate titration, 22%; C : H = 12 : 27·8. Calc. for $C_6H_{14}S$: C, 61·0; H, 11·9; S, 27·1; SH, 28%); the thiol in (i) was identified as (V) by its mercuric mercaptide, m. p. and mixed m. p. with synthetic sample (above) 74—75·5° (Found: C, 32·9; H, 6·05; Hg, 46·9%), by the green coloration in Rheinbold's test, and by the close identity of infra-red spectrum of (i) with that of synthetic (V); (ii) b. p. 50—77°/0·05 mm. (15·85 g.); and (iii) a final residue (3·90 g.) which was purified by chromatography on alumina to yield a reddish-brown oil consisting mainly of polymer of the type $C_6H_{13}{\cdot}S_x{\cdot}C_6H_{12}{\cdot}S_z{\cdot}C_6H_{13}$ [Found: C, 55·95; H, 9·65; N, 1·4; S, 33·1%; *M* (ebullioscopic in benzene), 351, 355, 364. Calc. for $C_{18}H_{38}S_4$: C, 56·5; H, 9·9; S, 33·5%; *M*, 382]; infra-red analysis of (iii) indicated that it was fully saturated.

Infra-red analysis of fraction (ii) showed the presence of traces of thiol and *NN*-diethylthioacetamide. A portion of (ii) was therefore purified by extraction first with 20% sodium hydroxide solution (2 × 25 ml.) and then with 50% hydrochloric acid (4 × 25 ml.), and the

product fractionated to give: (ii*a*) b. p. 50—65°/0·2 mm., n_D^{20} 1·4860 (Found: C, 62·6; H, 11·5; N, 0·27; S, 25·5%; *M* (ebullioscopic in benzene), 208. Calc. for $C_{12}H_{26}S_2$: C, 61·55; H, 11·1; S, 27·35%; *M*, 234]; and (ii*b*) b. p. 65—74°/0·2 mm., n_D^{20} 1·5055 [Found: C, 60·0; H, 10·8; N, 0·94; S, 28·95%; *M* (ebullioscopic in benzene), 225]. Fractions (ii*a*) and (ii*b*) are therefore mainly di-(1 : 1-dimethylbutyl) disulphide (VI; $x = 2$) together with minor amounts of the mono- and poly-sulphide; this was confirmed by the close identity of their infra-red spectra with that of synthetic (VI; $x \sim 4$); C:C type of unsaturation was absent. A band at 1536 cm.$^{-1}$ due to S=C–N probably indicated traces of the dithio-oxalodiamide $(Et_2N{\cdot}CS)_2$, since thioamides on being heated with sulphur and amines occasionally form this type of compound (cf. Levesque, U.S.P. 2,525,075, 1950).

Attempted Low-temperature Sulphurations.—(1) 2-Methylpent-2-ene (40 ml.) was added to the complex derived from *n*-butylamine (50 ml.) and sulphur (5·0 g.) in nitrogen. The complex was decomposed with ethanol at room temperature, and the mixture stirred for a further 30 min. Filtration of the product gave unreacted sulphur (4·7 g.) and a filtrate which on evaporation yielded no sulphurated product.

(2) A mixture of piperidine (15 g.), sulphur (5·0 g.), and 1-methyl*cyclo*hexene (25 g.) was refluxed in nitrogen for 5 hr. at 100°. The reddish liquid was decanted from some tar, the latter extracted with ligroin, and the ligroin solution of the main product extracted with cold hydrochloric acid. Fractionation of the neutral ligroin solution gave only unreacted olefin.

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The Reactions of Amines and Sulphur with Olefins. Part III. The Reaction of Diethylamine and Sulphur with* 1 : 5-*Diolefins.*

By R. W. Glazebrook and R. W. Saville.

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2 : 6-Dimethylocta-2 : 6-diene (I) with the sulphur–diethylamine combination at 140° yields mainly saturated cross-linked sulphides, RS_xR, where R contains thia*cyclo*pentane groups adjacent to the sulphide cross-link (x = 1 or 2), together with the cyclic sulphides (II) and (VI)—(VIII), formed by intramolecular sulphuration of (I). Infra-red spectroscopic evidence suggests the occurrence of similar cyclic structures in squalene polysulphide and in ebonite.

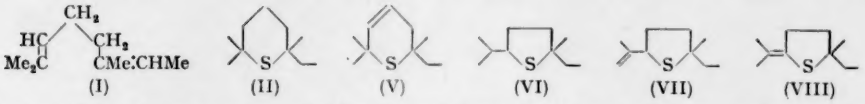
Farmer and Shipley (*J.*, 1947, 1519) first showed that the action of sulphur on 2 : 6-dimethylocta-2 : 6-diene (I) at 140° gives both a cyclic monosulphide formed by intramolecular sulphuration of the diolefin and an approximately equal proportion of a cross-linked polysulphide, RS_xR', which appeared to be analogous to the products obtained from sulphur and mono-olefins. Similar studies of the normal addition of hydrogen sulphide to (I) (Naylor, *J.*, 1947, 1532) showed that negligible cross-linked material is formed, the main product being 2-ethyl-2 : 6 : 6-trimethylthia*cyclo*hexane (II), together with smaller amounts of the intermediate monothiols (III) and (IV) (see p. 2096). Farmer and Shipley (*loc. cit.*) did not determine the detailed structures of their cyclic monosulphide fraction, the heterogeneity of which was to be expected in view of the numerous possible reaction courses by which the sulphuration reaction could proceed. However, infra-red analysis of their product revealed vinylidene unsaturation, $CH_2{:}CRR'$, and the apparent presence of 6-ethyl-2 : 2 : 6-trimethylthia*cyclo*hex-3-ene (V) as judged by comparison with (II) (Naylor, *loc. cit.*).

A logical extension of the work described in Parts I and II to determine the influence of amines on the structural pattern of the sulphur linkage in rubber–sulphur vulcanisates was to study the reaction of diethylamine and sulphur with (I) at 140°. The major

* Part I, *J.*, 1954, 2082. Part II, preceding paper.

products proved to be (1) a cyclic sulphide fraction and (2) a cross-linked polysulphide, in the approximate ratio of 1 : 2.

Constitution of the Cyclic Sulphide Fraction (1).—Infra-red analysis revealed the presence of (II), and of 2-ethyl-2-methyl-5-*iso*propylthia*cyclo*pentane (VI), but (V) appeared to be absent, as judged by the failure to detect unsaturation of the type *cis*-R·CH:CH·R′, and by comparison of the infra-red spectrum of (1) with that of the analogous 2 : 2 : 6 : 6-tetramethylthia*cyclo*hex-3-ene (Naylor, *J.*, 1949, 2749). The spectrum further revealed the presence of ~20% vinylidene unsaturation, CH_2:CRR′, and the absence of all other types



(I) (II) (V) (VI) (VII) (VIII)

of double bond. Subsequent behaviour on hydrogenation, however, indicated that further unsaturation must be present and, in fact, the ultra-violet absorption at ~2300 Å indicated the presence of the vinyl sulphide grouping C=C–S. It seemed highly probable that the latter was present as a tetrasubstituted double bond CRR′:CR‴·SR″, undetectable in the infra-red region, and that the above types of unsaturation were associated with the thia*cyclo*pentane structures (VII) and (VIII), respectively. This view was confirmed when catalytic hydrogenation of the cyclic sulphide fraction resulted in an increased proportion of (VI), while the amount of (II) present remained constant. Further, a sample of (1) which contained solely unsaturation of the type CRR′:CR‴·SR″ and was free from the saturated sulphides (II) and (VI), gave on catalytic hydrogenation, pure (VI).

Synthesis of Cyclic Sulphides.—The spectroscopic work necessitated synthesis of the cyclic sulphides (II), (VI), (VII), and (VIII). The first was prepared by the normal addition of hydrogen sulphide to (I), catalysed by 75% w/w sulphuric acid or aluminium bromide (cf. Arnold, B.P. 602,238; Van Riemsdijk, Van Stennis, and Waterman, *J. Inst. Petrol.*, 1951, **37**, 265). The second sulphide (VI) was prepared by the route :

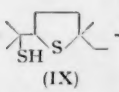
$$Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH \xrightarrow{Me{\cdot}CO{\cdot}SH} Me_2CH{\cdot}CH(S{\cdot}COMe){\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH$$

$$\xrightarrow{NaOMe} Me_2CH{\cdot}CH(SH){\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH \xrightarrow[H_2SO_4]{75\%\ w/w} (VI)$$

Synthesis of the unsaturated thia*cyclo*pentanes (VII) and (VIII) presented considerable difficulties and only partial success was achieved by the proposed route :

$$Me_2C{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH \xrightarrow{(SCN)_2} Me_2C(SCN){\cdot}CH(SCN){\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH$$

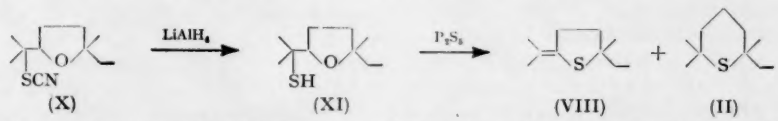
$$\xrightarrow{LiAlH_4} Me_2C(SH){\cdot}CH(SH){\cdot}CH_2{\cdot}CH_2{\cdot}CMeEt{\cdot}OH \xrightarrow{H_2SO_4}$$



(IX)

$$\xrightarrow[-H_2S]{AlBr_3} (VII) + (VIII)$$

Addition of dithiocyanogen to 3 : 7-dimethyloct-6-en-3-ol (cf. Wood, " Organic Reactions," Wiley, New York, 1946, Vol. III, p. 240) resulted unexpectedly in the immediate cyclisation of the dithiocyanato-adduct to give the cyclic ether (X). Reduction of the latter

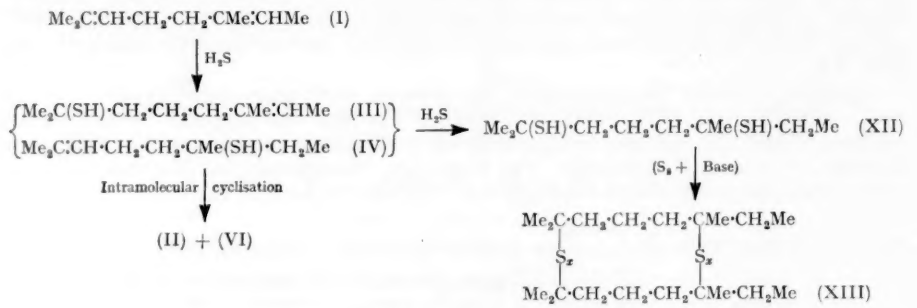


(X) (XI) (VIII) (II)

with lithium aluminium hydride (Backer and Strating, *Rec. Trav. chim.*, 1950, **69**, 638) gave a high yield of 2-ethyl-2 : 3 : 4 : 5-tetrahydro-5-(1-mercapto-1-methylethyl)-2-methylfuran (XI). Attempted replacement of the oxygen in (XI) by sulphur by reaction with phosphorus pentasulphide (Naylor, *J.*, 1947, 1106) led unexpectedly to a product containing neither thiol groups nor vinylidene unsaturation; it was mainly a mixture of (II) and

(VIII), the latter being probably formed by cleavage of the *tert.*-C–S bond in (XI) with elimination of hydrogen sulphide. Comparison of the infra-red spectrum of this product with that obtained from the reaction of (I) with diethylamine and sulphur revealed similarities. Cyclisation of the dithiocyanato-adduct to give the *six*-membered cyclic ether analogous to (X) appeared unlikely, as judged by the dissimilarity of the infra-red spectrum of the derived mercaptocyclic ether (XI) from those of known tetrahydropyrans (Naylor, *loc. cit.*); and stronger evidence for this view was provided by the fact that thiol elimination from a tetrahydromercaptopyran analogous to (XI) would have yielded (V), which was not present in the product. It seemed probable that (II) arose by ring-expansion during the reaction of (XI) with phosphorus pentasulphide, since Birch (*J. Inst. Petrol.*, 1953, **39**, 195) found that the high-temperature reaction of tetrahydrofurfuryl alcohol with hydrogen sulphide and alumina yields a mixture of thia*cyclo*hex-2-ene and thia*cyclo*hexane.

Constitution of the Cross-linked Polysulphide Fraction (2).—Elementary analysis and molecular-weight determination showed that fraction (2) consisted of two di-isoprene molecules for every 3 or 4 sulphur atoms, and infra-red analysis revealed that it was largely saturated and thiol-free. On this basis, it appeared initially that (2) consisted mainly of the polysulphide (XIII) formed by base-catalysed sulphur oxidation of the intermediate dithiol (XII), the latter resulting from addition of two molecules of hydrogen sulphide (formed by prior reaction of diethylamine with sulphur) to (I):

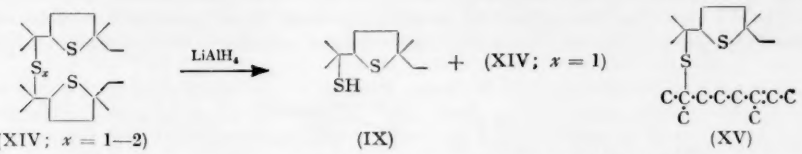


This apparently simple reaction course was subsequently shown to be invalid by the synthetic and degradative methods described below.

The dithiol (XII) was synthesised by the addition of toluene-ω-thiol to 3 : 7-dimethyloct-6-en-3-ol in the presence of 75% w/w sulphuric acid, followed by reductive cleavage of the resulting dibenzylthio-compound with sodium in liquid ammonia. This method considerably reduced the competing cyclisation of the diolefin encountered when (I) was used directly. Base-catalysed oxidation of (XII) with sulphur gave a saturated, thiol-free polysulphide of the type (XIII), or possibly of the polymeric chain type $R{\cdot}S_x{\cdot}R'{\cdot}S_x{\cdot}R'{\cdot}S_x{\cdot}R$, which had, however, a quite distinct infra-red spectrum from that of fraction (2).

Hydrogenolysis of the cross-linked polysulphide (2) with lithium aluminium hydride (Arnold, Lien, and Alm, *J. Amer. Chem. Soc.*, 1950, **72**, 731) gave (3) a high yield of an essentially saturated thiol $C_{10}H_{20}S_2$, and (4) a thiol-free product $C_{20}H_{38}S_{2\text{-}3}$. No hydrogen sulphide was formed during the hydrogenolysis, indicating that (2) was devoid of polysulphidic sulphur. The thiol value of (3) showed that only half the sulphur was present as a thiol group, and the low molecular weight (204) ruled out any possibility of a cross-linked structure containing two di-isoprene units. The remaining sulphur must therefore be present in cyclic sulphide form and, in fact, the infra-red spectrum of (3) was similar to that of the cyclic sulphide fraction (1), except for the presence of thiol groups and the absence of unsaturation. The structure of (3) as the mercaptothia*cyclo*pentane (IX) was finally established by the close identity of its infra-red spectrum with that of authentic (IX) obtained by addition of thiolacetic acid to (VIII) and subsequent hydrolysis of the acetyl-

thio-derivative. This leads to the view that the parent cross-linked polysulphide (2) consists mainly of the structures represented by (XIV) in which the cross-link is predominantly mono- and di-sulphidic. On this basis part of (2) should remain unaffected

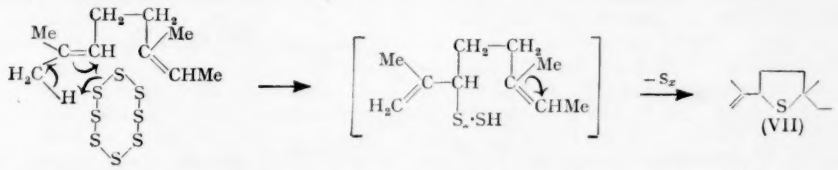


(XIV; x = 1—2) (IX) (XV)

by the hydrogenolysis and, in fact, infra-red examination of the thiol-free product (4) showed that it was closely similar to the original cross-linked polysulphide (2), and to (IX) except for the absence of a band due to the thiol group in the latter, and it must therefore be mainly (XIV; $x = 1$). The presence of a small amount of trialkylethylene unsaturation in (4) is attributed to the presence of minor amounts of structures such as (XV) formed by addition of (IX) to (I); the elementary analysis and intensity of the infra-red band due to RR'C:CHR'' are suggestive of (XIV; $x = 1$) and (XV) being present in (4) in the ratio of 4 : 1.

The structure (XIV) is clearly consistent with the mono- and di-sulphide cross-linked products obtained from the mono-olefins (Parts I and II). The isolation of *tert.*-alkanethiols from trialkylethylenes (Part II) led to a closer search for (IX) in the present reaction, and its presence was established in a small intermediate fraction between the main products (1) and (2).

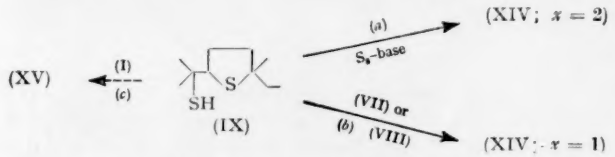
Reaction Mechanism.—A primary process in the sulphuration of (I) with the diethylamine–sulphur combination undoubtedly involves polar addition of hydrogen sulphide, formed by prior interaction of the diethylamine and sulphur, to (I). Polar cyclisation of the resulting *tert.*-thiols (III) and (IV) then gives the substituted thia*cyclo*hexane (II). To account for the substituted thia*cyclo*pentane (VII) and the main cross-linked product (XIV; x = 1—2) by a polar mechanism, it is necessary to envisage an electrophilic attack by sulphur at the unmethylated end of a double bond in (I) (cf. Van Veersen, *Rubber Chem. Tech.*, 1951, **24**, 169), followed by cyclisation of an intermediate mercapto-compound as suggested by :



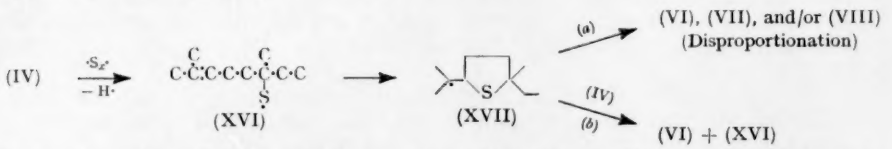
The analogous intermediate formed by the comparable attack of sulphur at the alternative double bond in (I) is unlikely to cyclise, since a seven-membered ring would result. Subsequent polar addition of hydrogen sulphide to (VII) yields (IX), and the latter undergoes (*a*) base-catalysed sulphur oxidation to give the major cross-linked polysulphide product (XIV; $x = 2$), (*b*) polar addition to the unsaturated cyclic sulphides (VII) or (VIII) to give (XIV; $x = 1$), or (*c*) polar addition to (I) to give (XV). In the presence of diethylamine, preferential oxidation of (IX) by path (*a*) will undoubtedly reduce RR'C:CHR'' unsaturation due to (XV) in the cross-linked product; (XV) is more likely to be obtained in higher proportion in sulphurations conducted in the absence of amine. A further important finding was that (VII) when heated with a catalytic amount of sulphur at 140° isomerises to (VIII), and this reaction may be responsible for the formation of (VIII) in the above experiments. Comparable isomerisations of allylic to vinylic sulphides have been effected by Tarbell and McCall (*J. Amer. Chem. Soc.*, 1952, **74**, 48).

The polar mechanism depicted above offers a self-consistent picture for the formation of most of the identified products and is in accordance with the reaction characteristics observed in the sulphuration of mono-olefins described in Parts I and II. The direct

combination of sulphur is supported by the virtual absence of cross-linked sulphides in the reaction of hydrogen sulphide with (I) (Naylor, *J.*, 1947, 1532) where sulphur is not available for the above type of attack. No adequate explanation can be offered for the formation of the saturated thia*cyclo*pentane (VI) by a polar mechanism, and thus one is forced to the view that free-radical sulphuration processes must participate to some extent. The co-existence of polar and free-radical mechanisms, capable of being influenced by small

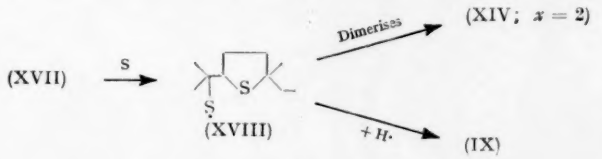


changes in experimental conditions, has been recognised by various workers (see Salomon, *Discuss. Faraday Soc.*, 1947, **2**, 353). The formation of (VI) can be explained by abnormal cyclisation of the open-chain alkylthio-radical (XVI), formed by loss of a hydrogen atom from the thiol (IV) on oxidation with sulphur. The resulting cyclic radical (XVII) may then be stabilised (*a*) by disproportionation to (VI) and (VII) or (VIII), or (*b*) by hydrogen-atom capture from the thiol (IV):



Naylor (*loc. cit.*) noted the reluctance of the thiol (IV) or (III) to cyclise by a polar mechanism to give (II) in the sulphur- or aluminium sulphide-catalysed addition of hydrogen sulphide to (I). Repetition of these experiments has now shown that the five-membered ring (VI) is also formed, possibly by the preferential cyclisation of (IV) in the above manner.

Free-radical attack of sulphur on (XVII) may also occur to a minor extent to give (XVIII), which may then dimerise to give (XIV; $x = 2$) or capture a hydrogen atom to give (IX):



It remains for future work to determine the relative importance of polar and free-radical mechanisms in sulphuration reactions of the present type.

Sulphuration of Polyisoprenes.—Many synthetic dialkyl tetrasulphides when boiled with sodium sulphite solution lose half their sulphur content, forming disulphides (Farmer and Shipley, *J.*, 1947, 1519; Bloomfield, *J.*, 1947, 1547), and Armstrong, Little, and Doak (*Ind. Eng. Chem.*, 1944, **36**, 628) showed that the polysulphide from sulphur and 2-methylbut-2-ene behaves likewise. On the other hand, Farmer, Shipley, and Bloomfield (*locc. cit.*) observed negligible removal of combined sulphur from the polysulphides of dihydromyrcene, geraniolene, and squalene. Such behaviour is to be expected if it is assumed that the latter possess only 1—2 sulphur atoms *in the cross-link* and the remainder in cyclic sulphide form, in contrast to the dialkyl polysulphides containing linear cross-links of more than 2 sulphur atoms. These considerations suggested that cyclic structures of the present type may be obtained from olefins containing more than 2 isoprene units, and therefore squalene polysulphide and ebonite were examined. The choice of ebonite in preference to soft-vulcanised rubber was made for two reasons: (*a*) For the identification of the cyclic sulphide

structures by infra-red methods, the material must contain about 30% of combined sulphur; and (*b*) for a true comparison with (XIV) the material must possess little residual unsaturation. Thus, although the use of infra-red analysis for the examination of conventional vulcanisates is very limited, these requirements are fulfilled by ebonite. The spectrum of (XIV) was compared with those of squalene polysulphide and ebonite, and distinct similarities were observed, notably a band of quite similar shape and intensity at 945 cm.$^{-1}$ in (XIV), 953 cm.$^{-1}$ in squalene polysulphide, and 947 cm.$^{-1}$ in ebonite, which was not present in the pure hydrocarbons. This band cannot be due, as believed by Sheppard and Sutherland (*J.*, 1947, 1699), to *trans*-RCH:CHR, which always occurs close to 965 cm.$^{-1}$ in allylic sulphides, but rather suggests the presence of cyclic structures of type (VI) in the above materials.

Experimental

Infra-red spectra were recorded on a Grubb-Parsons single-beam spectrometer. Ultraviolet light absorption measurements were made with absolute ethanol solutions by means of a Hilger Uvispek photoelectric spectrophotometer. Microanalyses were conducted under the supervision of Dr. W. T. Chambers.

2 : 6-*Dimethylocta*-2 : 6-*diene* (I).—This was prepared by reduction of purified geraniol with sodium and liquid ammonia; b. p. 56·0°/14 mm., n_D^{20} 1·4520 (Found: C, 86·85; H, 12·8. Calc. for $C_{10}H_{18}$: C, 87·0; H, 13·0%). Infra-red analysis revealed the absence of hydroxyl groups and less than 1% of vinylidene unsaturation, CH_2:CRR′. (I) was unchanged after 24 hours' heating at 140° with diethylamine or phenylhydrazine.

Synthesis of **2-*Ethyl*-2-*methyl*-5-iso*propylthia*cyclo*pentane*** (VI).—**3 : 7-*Dimethyloct*-6-*en*-3-*ol*.** Reaction of the Grignard reagent (25% excess) from magnesium (24 g.) and ethyl bromide (109 g.) with 6-methylhept-5-en-2-one (100 g.; b. p. 58—59°/10 mm., n_D^{20} 1·4420) in the usual manner gave the *tert.*-alcohol, b. p. 87°/12 mm., n_D^{20} 1·4548 (108 g.) (Found: C, 76·7; H, 13·0. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·8%).

4-*Hydroxy*-4-*methyl*-1-iso*propylhexyl thiolacetate*. The above *tert.*-alcohol (25 g.) reacted exothermally with freshly distilled thiolacetic acid (14 g.). After the initial reaction had subsided, the liquid was warmed on the steam-bath for 30 min. Distillation yielded the *thiolacetate*, b. p. 110—111°/0·01 mm. (34 g., 92%), n_D^{20} 1·4848 (Found: C, 61·9; H, 10·3; S, 13·8. $C_{12}H_{24}O_2S$ requires C, 62·0; H, 10·3; S, 13·8%).

3-*Mercapto*-2 : 6-*dimethyloctan*-6-*ol*. The thiolacetate (33 g.) was hydrolysed overnight in methanol (500 ml.) containing a trace of sodium methoxide. After removal of most of the solvent by distillation, water was added, and the liquid extracted with ether. Distillation gave the *hydroxy-thiol* (20 g., 73%), b. p. 61—62°/0·01 mm., n_D^{20} 1·4800 (Found: C, 62·9; H, 11·35; S, 16·9; SH, 17·4. $C_{10}H_{22}OS$ requires C, 63·2; H, 11·6; S, 16·85; SH, 17·4%). This (20 g.) was added slowly, with stirring, to 75% w/w sulphuric acid (100 g.) at 0°. The mixture was then allowed to reach room temperature and stirred for 15 min. Ice and water were added and the *thia*cyclo*pentane* (VI) was isolated in the usual manner, b. p. 87°/10 mm. (14 g., 77%), n_D^{20} 1·4765 (Found: C, 69·6; H, 11·5; S, 18·9. $C_{10}H_{20}S$ requires C, 69·8; H, 11·6; S, 18·6%): with chloramine-T it formed a *sulphidimine*, needles (from aqueous methanol), m. p. 135° (Found: C, 59·6; H, 8·1; N, 4·2; S, 18·4. $C_{17}H_{27}O_2NS_2$ requires C, 59·8; H, 7·9; N, 4·1; S, 18·8%), which depressed the m. p. of toluene-*p*-sulphonamide. Reaction of (VI) with peracetic acid in the usual manner gave a liquid *sulphone*, b. p. 88°/0·001 mm., n_D^{20} 1·4771 (Found: C, 59·0; H, 10·1; S, 15·6. $C_{10}H_{20}O_2S$ requires C, 58·9; H, 9·8; S, 15·7%).

Addition of Dithiocyanogen to **3 : 7-*Dimethyloct*-6-*en*-3-*ol*.**—Lead thiocyanate (36 g., 0·11 mol.) in dry chloroform (130 ml.) was cooled to 5—10°, and bromine (16 g., 0·1 mol.) in chloroform (50 ml.) added with vigorous stirring. The chloroform was decanted, and the residual solid washed with more solvent. The combined solutions were mixed with the *tert.*-alcohol (12·0 g., 0·08 mol.) in chloroform (20 ml.) at 10°, and kept overnight at room temperature. The yellow precipitate of polythiocyanogen was filtered off, and the chloroform solution diluted with ether, washed (water, thiosulphate, water), dried (Na_2SO_4), and fractionated. The **2-*ethyl*-2 : 3 : 4 : 5-*tetrahydro*-2-*methyl*-5-(1-*methyl*-1-*thiocyanatoethyl*)*furan*** had b. p. 62°/0·05 mm., n_D^{20} 1·4880 (7·5 g.) (Found: C, 61·85; H, 8·8; N, 6·7. $C_{11}H_{19}ONS$ requires C, 61·9; H, 8·9; N, 6·6%). The infra-red spectrum showed the absence of hydroxyl groups and unsaturation, but a band at 2160 cm.$^{-1}$ clearly indicated SCN. The remainder of the spectrum was consistent with the cyclic ether structure (X).

Use of phenyl iododichloride for the thiocyanation (cf. Neu, *Ber.*, 1939, **72**, 1505)

gave a light yellow liquid, b. p. 80°/0·08 mm., n_D^{20} 1·4870 (Found: C, 60·7; H, 8·65; N, 6·5%). The spectra of the two products were almost identical.

Reduction of (X).—This compound (3·4 g.) was added dropwise with vigorous stirring to lithium aluminium hydride (0·90 g., 2 equiv.) in dry ether (40 ml.). After refluxing for 15 min., the liquid was decomposed with ice and dilute sulphuric acid, and the usual method of isolation gave *2-ethyl-2 : 3 : 4 : 5-tetrahydro-5-(1-mercapto-1-methylethyl)-2-methylfuran* (XI), b. p. 88°/10 mm., n_D^{20} 1·4740 (2·8 g., 93%) (Found: C, 64·0; H, 10·65; S, 16·8; N, 0·2; SH, 17·6. $C_{10}H_{20}OS$ requires C, 63·8; H, 10·6; S, 17·0; SH, 17·5%). The spectrum of this colourless liquid was very similar to that of the original thiocyanato-compound (X) except for the replacement of the SCN band by that of SH at 2570 cm.$^{-1}$. Hydroxyl groups and unsaturation were again absent, and Rheinboldt's test indicated that (XI) was a *tert.*-thiol.

Action of Phosphorus Pentasulphide on (XI).—This compound (4·5 g.) and phosphorus pentasulphide (8·0 g.) were heated at $<10^{-3}$ mm. in a Carius tube for 6 hr. at 110°. The product was extracted repeatedly with ether and mixed with water, and the aqueous solution extracted. After drying, fractionation gave a liquid, b. p. 80°/12 mm., n_D^{20} 1·4922 (1·3 g.) (Found: C, 70·2; H, 11·0; S, 18·7. Calc. for $C_{10}H_{20}S$: C, 69·8; H, 11·6; S, 18·6. Calc. for $C_{10}H_{18}S$: C, 70·5; H, 10·65; S, 18·85%). Infra-red analysis revealed that thiol groups and vinylidene unsaturation $CH_2{:}CRR'$ were absent. Light absorption: max. 2275 Å; ε 1830 (for *M*, 170). The spectra were consistent with a mixture of (II) and (VIII), though >25% of C=C–S grouping, due to the latter, was present. The cyclic sulphides (V) and (VI) were absent from this product, but comparison of the spectrum with that of the cyclic sulphide fraction (I) from the reaction of sulphur–diethylamine with (I) revealed definite similarities.

2 : 6-Dibenzylthio-2 : 6-dimethyloctane.—3 : 7-Dimethyloct-6-en-3-ol (15·6 g., 0·1 mol.) was stirred vigorously at 0—5° with toluene-ω-thiol (24·8 g., 2 mol.) while sulphuric acid (100 g., 75% w/w) was added slowly (1 hr.). After a further hour's stirring at room temperature, decomposition with ice and the usual method of working up gave unchanged thiol (5·0 g.) and the *dibenzylthio*-compound, a colourless short-path distillate, n_D^{20} 1·5670 (10·9 g.) (Found: C, 74·5; H, 8·75; S, 17·0. $C_{24}H_{34}S_2$ requires C, 74·6; H, 8·8; S, 16·6%). The infra-red spectrum confirmed the absence of hydroxyl and thiol groups and also of olefinic unsaturation.

2 : 6-Dimercapto-2 : 6-dimethyloctane (XII).—The above dibenzylthio-compound (7·7 g., 0·02 mol.) in liquid ammonia (200 ml.) was cleaved with sodium (2·0 g., 1·1 equiv.) in the usual manner. After decomposition with ammonium chloride, the *dithiol* isolated had b. p. 119°/15 mm. (3·7 g., 90%), n_D^{20} 1·5017 (Found: C, 62·1; H, 10·35; S, 27·6. $C_{10}H_{22}S_2$ requires C, 58·3; H, 10·7; S, 31·0%). Rheinboldt's test indicated a tertiary thiol, and copper butyl phthalate estimation gave SH, 30·0 ($C_{10}H_{22}S_2$ requires SH, 32·0%). The infra-red spectrum revealed traces of the original dibenzylthio-compound as impurity, but refractionation gave a purer sample of the dithiol (XII), b. p. 112°/10 mm. (Found: C, 58·65; H, 10·4; S, 30·2%). No unsaturation could be detected.

Oxidative Cross-linking of (XII).—This dithiol (1·90 g.) was mixed with sulphur (0·2 g.) and diethylamine (0·1 g.). The polysulphide was isolated in the usual manner and purified by chromatography on silica gel. The spectrum bore no resemblance to that of the polysulphide (XIV) obtained from reaction of sulphur–diethylamine with (I).

Addition of Hydrogen Sulphide to (I).—(*a*) Hydrogen sulphide was passed rapidly into (I) (15 g.) in 75% w/w sulphuric acid (100 g.) at 0° with stirring during 4 hr. After addition of ice, the product isolated contained thiol (SH, 6·6%). Removal of the latter with copper butyl phthalate and fractionation gave (II), b. p. 81—82°/10 mm., n_D^{20} 1·4857 (Found: C, 70·0; H, 11·8; S, 18·3. Calc. for $C_{10}H_{20}S$: C, 69·8; H, 11·6; S, 18·6%). The yield was never >10% owing to the cyclisation of (I).

(*b*) A rapid stream of dry, purified hydrogen sulphide was passed into a solution of freshly sublimed aluminium bromide (2·0 g.) in carbon disulphide (50 ml.) while (I) (20 ml.) was simultaneously added during 1 hr. Fractionation of the isolated product gave: (i) b. p. 70°/12 mm. (6·1 g.), n_D^{20} 1·4772 (Found: C, 75·7; H, 12·5; S, 12·1%); (ii) b. p. 70—80°/12 mm. (4·5 g.), n_D^{20} 1·4880 (Found: C, 69·4; H, 11·65; S, 18·6. Calc. for $C_{10}H_{20}S$: C, 69·8; H, 11·6; S, 18·6%); (iii) b. p. 80—120°/12 mm. (3·0 g.), n_D^{20} 1·4922 (Found: C, 68·3; H, 11·65; S, 19·35%); (iv) b. p. 120°/12 mm. (1·90 g.), n_D^{20} 1·4950 (Found: C, 62·1; H, 10·95; S, 25·6%). The infra-red spectra revealed that all the fractions were saturated; the main constituent of (i)—(iii) was (II), with the dithiol (XII) in minor amount, fractionation failing to effect complete separation. The intensity of the SH band in (iv) indicated that the dithiol was the major constituent (Found: SH, 24·8. Calc. for $C_{10}H_{22}S_2$: SH, 31·0%).

Action of Sulphur on (I) *in the Presence of Diethylamine.*—The diene (I) (50·0 g.) and diethyl-

amine (30·0 g.) were heated with sulphur (10·0 g.) at $<10^{-3}$ mm. in a Carius tube for 20 hr. at 140° ± 1°. The resulting dark brown liquid, which contained no tar and negligible amine hydrogen sulphide, was washed out with ligroin, and material of low b. p. removed on the steam-bath in nitrogen. Fractionation of the residue gave unchanged (I) (25·1 g.), b. p. 68—84°/20 mm., n_D^{20} 1·4530, containing a trace of sulphide (Found: S, 1·43%), and the products in three main fractions: (i) b. p. 84—96°/20 mm. (8·3 g.), n_D^{20} 1·4920 (Found: C, 70·7; H, 11·15; N, 0·8; S, 16·95. Calc. for $C_{10}H_{18}S$: C, 70·5; H, 10·65; S, 18·85. Calc. for $C_{10}H_{20}S$: C, 69·8; H, 11·6; S, 18·6%); (ii) b. p. 48—65°/0·03 mm. (12·1 g.), n_D^{20} 1·5300; and (iii) a final residue, not distillable below 140°/0·03 mm. (18·0 g.). The infra-red spectrum of the recovered olefin showed negligible $CH_2{:}CRR'$ unsaturation, indicating the absence of appreciable isomerisation or cyclisation.

Infra-red analysis of the cyclic sulphide fraction (i) indicated ~20% of $CH_2{:}CRR'$ groups due to (VII) and only traces of *N*-ethylthioacetamide and (I). Negligible trialkylethylene unsaturation was detected and the absence of (V) was confirmed by comparison with the spectrum of the analogous 2 : 2 : 6 : 6-tetramethylthia*cyclo*hex-3-ene. The presence of the saturated cyclic sulphides (II) and (VI) was confirmed, while the ultra-violet spectrum indicated ~40% of C=C–S grouping due to (VIII) in this fraction (i). Thiol groups were absent. Mercuric chloride gave a white, solid derivative insoluble in all common solvents.

Addition of ligroin to (ii) precipitated an orange-red layer, b. p. 54—62°/0·1 mm. (3·1 g.), n_D^{20} 1·5450 (Found: C, 52·9; H, 9·55; N, 10·3%). The spectrum and chemical reactions indicated mainly *N*-ethylthioacetamide, negligible olefin sulphides being detectable. The main ligroin solution from (ii) was extracted with 50% hydrochloric acid (4 × 25 ml.), dried, and distilled, giving: (*a*) b. p. 40°/0·1 mm. (1·85 g.), n_D^{20} 1·5000 (Found: C, 68·5; H, 10·6; N, 0·06; S, 20·8%); (*b*) b. p. 50—60°/0·1 mm. (2·4 g.), n_D^{20} 1·5172 (Found: C, 64·05; H, 10·0; N, 0·17; S, 25·7; SH, 7·0%); and (*c*) b. p. 60—65°/0·1 mm. (1·2 g.), n_D^{20} 1·5270 [Found: C, 60·2; H, 9·6; N, 0·47; S, 30·35; SH, 9·0%; *M* (ebullioscopic in benzene), 190]. The thiol values of (*b*) and (*c*) were determined argentometrically as copper butyl phthalate titration gave indefinite end-points; Rheinboldt's test indicated tertiary thiol in both cases. Infra-red analysis revealed negligible $CH_2{:}CRR'$ groups and <10% of trialkylethylene-type unsaturation. The fractions were otherwise saturated, containing a large proportion of the cyclic thiol-sulphide (IX) (Calc. for $C_{10}H_{20}S_2$: C, 58·8; H, 9·8; S, 31·4; SH, 16·2%; *M*, 204). The thiol value of (*c*) indicated 56% of (IX) and infra-red analysis gave ~60%.

The final residue (iii) (18·0 g.) was dissolved in excess of ligroin and extracted with 50% hydrochloric acid (4 × 25 ml.) and further purified by chromatography on silica gel; ~95% of the resulting clear, yellow oil distilled at 120—140° in a short-path still, two typical fractions only being recorded: (*a*) n_D^{20} 1·5312 [Found: C, 63·15; H, 10·0; S, 26·8%; *M* (ebullioscopic in benzene), 310]; and (*b*) n_D^{20} 1·5395 (Found: C, 62·75; H, 10·0; S, 27·4%; *M*, 405). Infra-red analysis showed that the major product was thiol-free and saturated; bands at 1670 cm.$^{-1}$ and 827 cm.$^{-1}$ indicated 7—10% of $RCH{:}CR'R''$ (two $RCH{:}CR'R''$ groups per mol.). A small proportion (~12%) of C=C–S was, however, present (light absorption: max. 2350 Å; ε 940), indicative of tetrasubstituted double bonds.

A further reaction for 6 hr. at 140° ± 1° with sulphur (5·0 g.), diethylamine (15·0 g.), and (I) (40·0 g.) gave the cyclic sulphide fraction (7·5 g.) containing thioamides, which on acid extraction and fractionation gave: (i) b. p. 88—94°/15 mm. (2·9 g.), n_D^{20} 1·4961 [Found: C, 71·55; H, 10·85; N, 0; S, 16·65; *M* (ebullioscopic in benzene), 156, 159]; and (ii) b. p. 100—125°/15 mm. (2·94 g.), n_D^{20} 1·5155 (Found: C, 65·85; H, 9·65; N, 0·54; S, 22·6%; *M*, 178, 181). A trace of the di-isoprene (I) was present in (i). A band at 890 cm.$^{-1}$ due to $CH_2{:}CRR'$ groups in the infra-red spectra of (i) and (ii) suggested that more of (VII) was obtained in this shorter reaction period, the amount of (VII) in (i) and (ii) being 40% and 30% respectively. The saturated ring (II) was present in both fractions, but neither (V) nor (VI) was detectable. Ultra-violet examination was not carried out in this experiment. The polysulphide residue (8·1 g.) was purified by chromatography on alumina (Found: C, 59·55; H, 9·9; N, 0·11; S, 30·5. Calc. for $C_{20}H_{38}S_4$: C, 59·1; H, 9·4; S, 31·5%). The presence of only mono- and di-sulphide cross-links in this material (cf. XIV) was confirmed by sulphite treatment. Thus, the total sulphur loss (cf. Farmer and Shipley, *loc. cit.*) was 1·4% (5 hr. at 100°, using 10% sodium sulphite solution).

Reactions of the Cyclic Sulphide Fraction (i).—(a) *Hydrogenation.* The sample used had b. p. 85—90°/10 mm., n_D^{20} 1·4887 (Found: C, 70·5; H, 11·35; S, 18·2%; C : H, 10 : 19·3). Infra-red analysis revealed 15% of $CH_2{:}CRR'$. The sample (3·04 g.), when hydrogenated over palladium on charcoal (Bateman and Shipley, forthcoming publication), absorbed 240 ml. of

hydrogen (N.T.P.); unsaturation, 60%/mol. The product, b. p. 85—87°/10 mm., n_D^{20} 1·4800 (Found: C, 70·0; H, 11·65; S, 18·4. Calc. for $C_{10}H_{20}S$: C, 69·8; H, 11·6; S, 18·6%), contained no thiol, but infra-red analysis showed that it consisted of (II) and (VI); the amount of the former had remained constant but that of the latter had increased. A second sample of cyclic sulphide, free from (II) and (VI) by fractional elution from silica gel and shown by infra-red analysis to contain only CRR'·CR''':CR''·SR''-type unsaturation due to (VIII), was similarly hydrogenated. The theoretical amount of hydrogen was absorbed (one double bond per molecule), and infra-red analysis of the product revealed pure (VI).

(b) *Reaction with thiolacetic acid.*—The cyclic sulphide sample used contained both (II) and (VI) but the unsaturation was almost entirely due to (VIII), being of the tetrasubstituted type. Freshly distilled thiolacetic acid (10·0 g.) and the cyclic sulphide sample (15·0 g.) were irradiated with ultra-violet light for 7 hr. at 15°. Distillation yielded: (i) unchanged acid (9·0 g.), b. p. 85—90°/760 mm.; (ii) saturated cyclic sulphide, b. p. 80—90°/10 mm. (12·0 g.), shown by infra-red analysis to be a mixture of (II) and (VI) unaffected by irradiation; and (iii) the thiolacetate, b. p. 73—77°/0·01 mm. (3·1 g.). Hydrolysis of the ester with aqueous-ethanolic potassium hydroxide under nitrogen gave *2-ethyl-5-(1-mercapto-1-methylethyl)-2-methylthiacyclopentane* (IX), b. p. 48—50°/0·01 mm., n_D^{20} 1·5160 (Found: C, 58·8; H, 9·85; S, 31·0; SH, 16·1. $C_{10}H_{22}S_2$ requires C, 58·8; H, 9·8; S, 31·4; SH, 16·2%), presence of the five-membered ring being confirmed by comparison of the infra-red spectrum with that of (VI).

(c) *Isomerisation.* A sample of cyclic sulphide containing 14% of CH_2:CRR' unsaturation due to (VII) was heated *in vacuo* with a catalytic amount of sulphur for 48 hr. at 140°. The infra-red spectrum of the product revealed 7% of CH_2:CRR' unsaturation, no other appreciable change being detected. The ultra-violet spectrum indicated that ε_{2300} increased from ~1100 to ~1700 during the heating, the increase being due to 7% of C=C–S chromophore. A blank experiment omitting sulphur confirmed the absence of purely thermal isomerisation of (VII) to (VIII).

In these experiments, the estimates of the C=C–S grouping were based on the highest extinction coefficient with max. (ethanol) 2290 Å [ε 7750 was recorded for samples of (VIII) which contained no other type of unsaturation (cf. also Koch, *J.*, 1949, 387)].

Reactions of the Cross-linked Polysulphide Fraction (iii).—*Hydrogenolysis.* The main sulphide fraction (iii) from reaction of (I) with sulphur–diethylamine (20 hr. at 140°) was purified by chromatography on silica gel and by molecular distillation; it had n_D^{20} 1·5390 [Found: C, 62·7; H, 10·0; S, 27·6%; *M* (ebullioscopic in benzene), 400], corresponding to 2 olefin units per 3—4 sulphur atoms. The infra-red spectrum revealed 6—10% of RCH:CR'R'' groups (two RCH:CR'R'' groups/mole), and CH_2:CRR'-type unsaturation was absent. Lithium aluminium hydride (1·50 g.) was stirred rapidly at room temperature with tetrahydrofuran (50 ml.) while (iii) (4·0 g.) was slowly added, the mixture then being refluxed for 4 hr. After decomposition with ice and 2N-sulphuric acid, two main fractions were isolated:

(*a*) B. p. 60—65°/0·5 mm. (55·0°/0·1 mm.) (2·4 g.), n_D^{20} 1·5168 [Found: C, 59·0; H, 10·0; S, 31·25; SH, 17·6%; *M* (ebullioscopic in benzene), 204. $C_{10}H_{20}S_2$ requires C, 58·8; H, 9·8; S, 31·4; SH, 16·2%; *M*, 204]. The *thiol* was largely saturated, the spectrum revealing <10% of RCH:CR'R'' (one C:C per/*M* = 204). Comparison of the infra-red spectrum of (*a*) with those of (XII) and 3:7-dimercapto-2:6-dimethyloctane (Cunneen, *J.*, 1947, 139) confirmed that the latter two dithiols were absent. Comparison with the cyclic thiol-sulphide (IX) obtained from the reaction of thiolacetic acid with the cyclic sulphide fraction revealed that the two were almost identical. Excess of 10% mercuric cyanide with (*a*) in ethanol gave an oil which could not be crystallised, and aluminium bromide with (*a*) in benzene gave an immediate evolution of hydrogen sulphide.

Fraction (*b*) was a clear, yellow short-path distillate (1·30 g.), n_D^{20} 1·5185 [Found: C, 65·7; H, 10·6; S, 23·9; SH < 1%; *M* (ebullioscopic in benzene), 338]. The infra-red spectrum was practically identical with that of the cyclic thiol-sulphide (IX), apart from the SH band; RCH:CR'R'' type unsaturation (20%) probably due to (XV) was present [Calc. for $C_{20}H_{38}S_2$: C, 70·1; H, 11·1; S, 18·7. Calc. for $C_{20}H_{38}S_3$: C, 64·2; H, 10·2; S, 25·9. Calc. for (XIV; $x = 1$) and (XV) in the ratio 1 to 4: C, 65·5; H, 10·4; S, 23·5%].

The ultra-violet spectrum of the cleavage thiol (*a*) above showed little greater absorption than expected for a saturated sulphide with two sulphur atoms.

Squalene Polysulphide.—Squalene (13·0 g.), purified by molecular distillation, and sulphur (1·4 g.) were heated for 8 hr. at 140° ± 1° *in vacuo* (cf. Bloomfield, *J.*, 1947, 1546). The product was distilled in a short-path still for 8 hr. at 140°, and the infra-red spectrum of the residual polysulphide examined for cyclic sulphide structures.

Ebonite.—Samples containing ~32% of sulphur were prepared from pale crepe by Mr. R. I. Wood, in very thin sheets suitable for spectroscopic examination. No auxiliary accelerators or ebonite dust were incorporated. The infra-red spectra of 5-hr. and 30-hr. vulcanisates were identical and unaltered by acetone extraction. The ebonite spectra were compared with those of the cross-linked sulphide (XIV) from (I) and of squalene polysulphide. Distinct similarities were apparent, in particular a band at 945 cm.$^{-1}$ in (XIV), 953 cm.$^{-1}$ in squalene polysulphide, and 947 cm.$^{-1}$ in ebonite, of quite similar shape and intensity in all three which was not present in the pure hydrocarbons. The band appeared to be related to the 958, 942 cm.$^{-1}$ doublet in (VI) and to the 947 cm.$^{-1}$ band in (IX), strongly suggesting the presence of this type of grouping.

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N-*Ethyl*(*or* -*Methyl or* -*Phenyl*)-N-2-*halogenoethyl*-1(*or* -2)-*naphthylmethylamines. Part II.* Chemical Reactivity and Pharmacological Activity.*

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Graphs are presented showing the behaviour of some of the compounds mentioned in the title in acetone–water (2 : 1) at 30·0°. The bromo- and iodo-compounds of the *N*-ethyl (or *N*-methyl) series lose their halogen almost instantaneously, and there is evidence that a *N*-substituted ethyleneiminium ion is first produced, which is then destroyed more or less rapidly, mainly by hydrolysis. With the chloro-compounds loss of chlorine is incomplete, but the same general features of the reactions are observed. Biological assays, at appropriate times, of solutions prepared as for kinetic experiments give values lying close to the chemically determined curves recording the life-history of the ethyleneiminium ions formed (cf. Graham and Lewis, *Brit. J. Pharmacol.*, 1954, **9**, 68). This provides the first explicit evidence that ethyleneiminium ions are formed and are probably the pharmacologically active species in the antiadrenaline and antihistamine action of these compounds. The mechanism of formation of these ions and their structure are also discussed. Some evidence about the behaviour of dibenamine is also recorded. The fluoro-compounds and the *N*-phenyl compounds decompose very slowly or not at all in aqueous acetone at 30°.

In Part I* the variation of pharmacological properties with structure of the compounds mentioned in the title was discussed with special reference to mobility of the halogen. The kinetics of the decomposition of some of these compounds in acetone–water (2 : 1) at 30·0° are now presented graphically in Figures 1—5. We did not attempt to determine the details of the kinetics, or to evaluate rate coefficients, because of the complexity of the systems. Our objects were to correlate pharmacological properties with the mobility of the halogen, to provide evidence of the formation of *N*-substituted ethyleneiminium ions when the halogeno-amines were liberated from their salts, and to obtain solutions of these ions of definite but varied concentration for pharmacological assay. We have thus provided cogent evidence that in this range of compounds the substituted ethyleneiminium ion is the pharmacologically active species, a hypothesis advanced by Nickerson and Gump (*J. Pharmacol.*, 1949, **97**, 25). A preliminary account of this work has appeared already (Chapman, James, Graham, and Lewis, *Chem. and Ind.*, 1952, 805). Nickerson and Gump

* Part I, *J.*, 1953, 1865.

(*loc. cit.*) advanced their hypothesis by analogy with the behaviour of the aliphatic bis-2-chloroethylamines (" nitrogen mustards ") which have been thoroughly investigated by Hanby, Hartley, Powell, and Rydon (*J.*, **1947**, **519**), by Golumbic, Fruton, and Bergmann (*J. Org. Chem.*, **1946**, **11**, 518), and by Bartlett, Ross, and Swain (*J. Amer. Chem. Soc.*, **1947**, **69**, 2971, 2977).

Experimental

Materials.—The halogeno-amine salts were prepared and purified as in Part I, analytically pure samples being used. " AnalaR " acetone was diluted with distilled water for solvent.

Procedure.—The finely powdered salt (4 mmoles) was dissolved in water (50 c.c.) in a 200 c.c. flask, and acetone was (132 c.c.) added. The quantity of 0·400N-sodium hydroxide solution calculated to neutralise exactly the combined halogen hydracid was added, the time of half-addition being taken as the zero for the reaction. The solution (0·02M) was made up to the mark with water and placed in a thermostat at 30°. Aliquot portions (5 c.c.) were withdrawn at intervals (syringe pipette) and run into water (30 c.c.) covered with ether (20 c.c.), thus arresting the reaction and removing unchanged halogeno-compound. The aqueous layer and washings were titrated as follows: (*a*) chloride ions were determined by the Volhard method, bromide ions by a modified Volhard method (Kolthoff and Stenger, " Volumetric Analysis," New York, 1947, Vol. II, p. 272), and iodide ions by silver titration with dichlorofluorescein as indicator; (*b*) ethyleneiminium ions were determined by the iodine–thiosulphate titration developed by Golumbic *et al.* (*loc. cit.*) save that the reaction mixture was set aside with a five-fold excess of thiosulphate for 30 min. before back-titration, and a control determination was included; and (*c*) hydrogen ions formed were determined by titration of 0·0500N nitric acid (10·0 c.c.) and pure ethanol (30 c.c.) with 0·0500N-sodium hydroxide, in the presence and in the absence of the extracted aliquot portion, phenolphthalein being used as indicator (Simonetta, di Modrone, and Favini, *Gazzetta*, **1950**, **80**, 129). In the acid titrations it was shown that the presence of the alcohol corresponding to the halogeno-amines did not affect the titre.

The fluoro-compounds and derivatives of *N*-phenyl-1-naphthylmethylamine were weighed as free bases. Only ethyleneiminium-ion determinations were attempted with the fluoro-compounds.

Isolation of Picrylsulphonates of Ethyleneiminium Ions.—To a solution of *N*-2-bromoethyl-*N*-ethyl-1′-naphthylmethylamine in aqueous acetone, prepared as for kinetic experiments but of greater concentration, was added immediately an excess of acidified aqueous sodium picrylsulphonate (pH 2). The mixture was cooled to 0° and the solid product filtered off and recrystallised from aqueous acetone. N-*Ethyl*-N-1-*naphthylmethylethyleneiminium picrylsulphonate monohydrate* had m. p. 149—150° [Found: C, 49·5; H, 4·0; N, 10·7; S, 6·2; H_2O, 1·8 (loss in wt.). $C_{21}H_{20}O_9N_4S,H_2O$ requires C, 49·1; H, 4·1; N, 10·9; S, 6·2; H_2O, 1·8%]. The picrylsulphonate of the corresponding alcohol had m. p. 193° and, on admixture with the above, m. p. 145—155°. The following picrylsulphonates were similarly prepared. N-*Methyl*-N-1-*naphthylmethylethyleneiminium picrylsulphonate sesquihydrate*, m. p. 154° (Found: C, 46·7; H, 3·8; N, 10·7; S, 5·9. $C_{20}H_{18}O_9N_4S,1·5H_2O$ requires C, 46·4; H, 4·0; N, 10·8; S, 6·2%). N-*Ethyl*-N-2-*naphthylmethylethyleneiminium picrylsulphonate dihydrate*, m. p. 192° (Found: C, 46·9; H, 4·1; N, 10·0; S, 5·9. $C_{21}H_{20}O_9N_4S,2H_2O$ requires C, 46·7; H, 4·4; N, 10·4; S, 5·9%). N-*Methyl*-N-2-*naphthylmethylethyleneiminium picrylsulphonate sesquihydrate*, m. p. 193—194° (Found: C, 47·0; H, 4·0; N, 10·5; S, 6·1%).

Discussion

The reactions of the *N*-2-halogenoethyl-*N*-phenyl-1′-naphthylmethylamines were studied at 30° in acetone–water (4 : 1 or 8 : 1) because of their insolubility in the usual medium. Under these conditions halide ions were liberated very slowly and thiosulphate-consuming products were not formed (see Table). In acetone–water (2 : 1) the *N*-ethyl-(or *N*-methyl)-*N*-2-fluoroethyl-1′-naphthylmethylamines behaved similarly.

Fig. 1 shows behaviour typical of all the chloro-compounds investigated, save the *N*-phenyl compounds. Chloride was liberated at a measurable rate throughout, and ultimately equilibrium was attained, usually at about 80% decomposition. The curves showing the development and decay of a thiosulphate-consuming species, probably an ethyleneiminium ion, all have a maximum of varying magnitude (cf. Table). The hydrogen-ion concentration increased steadily from zero initially, but did not attain a final value

corresponding to complete destruction of the ethyleneiminium ion by water, nor did the amount of hydrogen ion produced at any time correspond exactly to the difference between the amount of halogeno-amine transformed and the amount of ethyleneiminium ion persisting (Fig. 1). Fig. 2 shows the characteristic behaviour of two bromo-compounds: *N*-2-bromoethyl-*N*-ethyl-1′- (curves *A*, *B*, and *C*) and -2′-naphthylmethylamine. The first provides clear evidence of the formation of ethyleneiminium ions from bromo-compounds of this type, since the substituted bromoethylamine lost almost all its bromine virtually instantaneously, only a little hydrogen ion being formed during the same period, and a quantity of a thiosulphate-consuming compound approximately equivalent to the liberated bromide was also produced. Unfortunately it was impossible to standardise thiosulphate against a pure ethyleneiminium salt because the only available salts were insoluble. However, there is evidence that piperazinium salts do not consume thiosulphate (Allen, unpublished work), so that the only transformation of the bromoethylamine which will, in the limit, satisfy these conditions is: $R_2N{\cdot}CH_2{\cdot}CH_2Br \rightleftharpoons R_2\overset{+}{N}{<}[CH_2]_2 + Br^-$. Moreover, the ethyleneiminium curve "follows" the bromide ion curve in its rapidly ascending phase (Fig. 2), and then shows a characteristic decline in which reaction with water predominates. During the first few minutes, the sum of the amounts of hydrogen ion and ethyleneiminium ion was, within experimental error, equal to the amount of bromide ion liberated, as expected, but in view of the rapidity of these reactions in the early stages no

Reactions and properties of 1-$C_{10}H_7{\cdot}CH_2{\cdot}NR{\cdot}CH_2CH_2X$.‡

Compound R	X	Maximum proportion of X^- liberated, % (usually after ~22 hr.)	Maximum proportion of ethylene-iminium ion formed, %	Antiadrenaline activity * μmoles/kg.	Antihistamins activity † μmoles/kg.
Ph	Cl	(*a*) 0 (*b*) 0·8	0	Inactive	Inactive
Ph	Br	(*a*) 1·6 (*b*) 8	0	,,	,,
Ph	I	(*a*) 0 (*b*) 1·3	0	,,	,,
Et	F	0 §	0	,,	,,
Et	Cl	87	34	0·60	0·92
Et	Br	100	86	0·62	0·78
Et	I	100	100	1·22	0·66
Me	F	0 §	0	Inactive	Inactive
Me	Cl	96	18	79·3	,,
Me	Br	100	100	1·31	4·79
Me	I	100	47	9·21	2·96

(*a*) After 4 hr., (*b*) after 22 hr. in acetone–water (4 : 1 for X = Cl, Br; 8 : 1 for X = I).

Reactions and properties of 2-$C_{10}H_7{\cdot}CH_2{\cdot}NR{\cdot}CH_2{\cdot}CH_2X$.‡

Et	F	0 §	0	Inactive	Inactive
Et	Cl	77	47	31·3	23·8
Et	Br	100	96	14·2	22·8
Et	I	99	79	9·6	17·4
Me	F	0 §	0	Inactive	Inactive
Me	Cl	82	15	,,	,,
Me	Br	89	72	18·8	26·5
Me	I	100	53	11·9	35·6

* $E.D._{99}$ Spinal cat. † $E.D._{75}$ Chloralosed cat.
‡ Except where R = Ph and X = F, the compounds were administered as HX salts.
§ Qualitative tests only were done.

exact quantitative significance is ascribed to this. After about 1300 min. the ethyleneiminium ion had disappeared and the hydrogen-ion and bromide-ion concentrations were equivalent, corresponding closely with the simplest type of behaviour, *viz.*:

$$R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}Br \rightleftharpoons \bar{B}r + R_2\overset{+}{N}\!\begin{array}{l}\diagup CH_2\\ \\ \diagdown CH_2\end{array} \xrightarrow{H_2O} R_2N{\cdot}CH_2{\cdot}CH_2{\cdot}OH + H^+$$

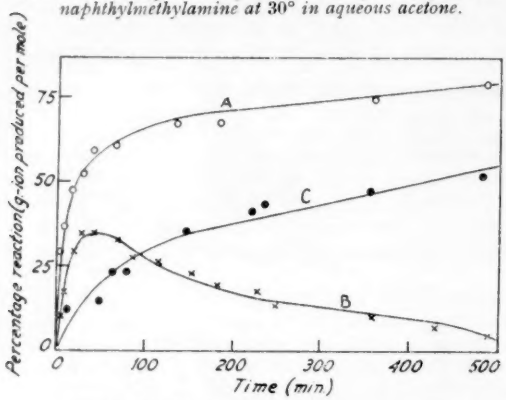
This requires the ethyleneiminium- and hydrogen-ion curves to be symmetrical about the abscissa through their intersection. Departures from this behaviour may be due to

errors in the hydrogen-ion determinations. Curves *A'*, *B'*, and *C'* show the same features, save that the substituted bromoethylamine decomposed more gradually after a rapid initial phase. This may be due to rapid attainment of an initial equilibrium, followed by a slow further decomposition :

We consider the sigmoid character of the hydrogen-ion curve to be fortuitous.

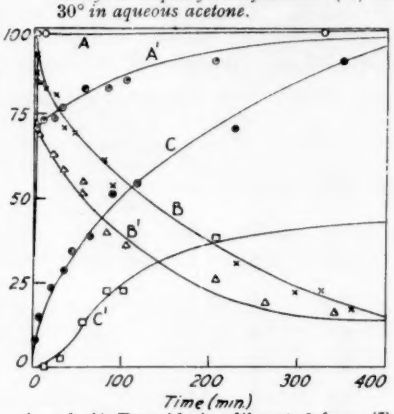
Fig. 3 shows the behaviour of *N*-ethyl-*N*-2-iodoethyl-1'-naphthylmethylamine (*A*, *B*, *C*) and of the corresponding 2'-compound (*A'*, *B'*, and *C'*). The first compound behaved more as the simplest type than the corresponding bromo-compound, whereas the second group of curves shows that among 2'-compounds even the iodo-derivatives behaved in a way characteristic of incomplete initial decomposition, as seen most strikingly with the chloro-

FIG. 1. *Decomposition of* N-2-*chloroethyl*-N-*ethyl*-1'-*naphthylmethylamine at* 30° *in aqueous acetone.*



A, Chloride ion liberated.
B, Ethyleneiminium ion formed.
C, Hydrogen ion formed

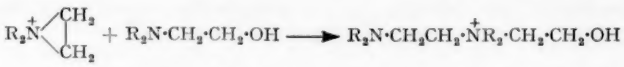
FIG. 2. *Decomposition of* N-2-*bromoethyl*-N-*ethyl*-1'- (I) *and* N-2-*bromoethyl*-N-*methyl*-2'-*naphthylmethylamine* (II) *at* 30° *in aqueous acetone.*



A and *A'*, Bromide ion liberated from (I) and (II) respectively.
B and *B'*, Ethyleneiminium ion formed from (I) and (II) respectively.
C and *C'*, Hydrogen ion formed from (I) and (II) respectively.

compounds. The other bromo- and iodo-compounds of the series behaved in a manner governed, apart from minor differences (cf. Table), by the same principles as those set out above.

Fig. 4 shows that at 0°, with a reactive substituted bromoethylamine, the liberation of bromide ion and formation of ethyleneiminium ion pursued closely similar courses, but that raising the temperature caused rapid destruction of the ethyleneiminium ion. Fig. 5 shows the effect of adding the alcohol corresponding to the bromo-compound on the decomposition of the ethyleneiminium ion. It is on the basis of this observation that we believe that the decomposition of the ethyleneiminium ion usually involves not only hydrolysis, but also the reaction :



The various determinations upon which all these curves are based are subject to considerable experimental error, although less than that involved in the biological assays (p. 2108). However, the observations recorded give a good general picture of the trend of events in aqueous-acetone solutions of the halogeno-amines in question.

We attempted to isolate, as picrylsulphonates, the ethyleneiminium ions formed in these reactions. *N*-Ethyl-*N*-1-naphthylmethylethyleneiminium picrylsulphonate was isolated as a crystalline monohydrate and gave satisfactory analyses. The remaining picrylsulphonates are also thought to be hydrated, but the analyses are less satisfactory. However, the mode of preparation and mixed m. p. determinations preclude the alternative formulation of these compounds, *viz.*, as *N*-disubstituted 2-hydroxyethylamine picrylsul-

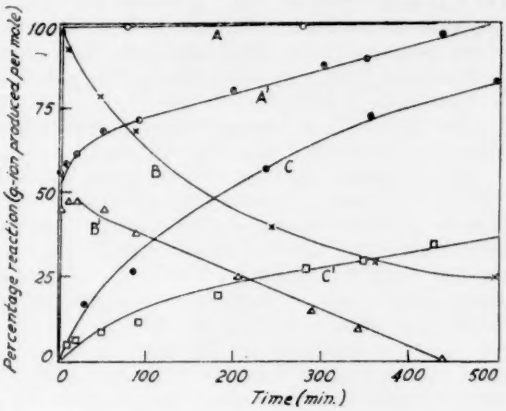


FIG. 3. *Decomposition of* N-*ethyl*-N-2-*iodoethyl*-1′- (III) *and* N-*ethyl*-N-2-*iodoethyl*-2′-*naphthylmethylamine* (IV) *at* 30° *in aqueous acetone.*

A and *A′*, Iodide ion liberated from (III) and (IV) respectively.
B and *B′*, Ethyleneiminium ion formed from (III) and (IV) respectively.
C and *C′*, Hydrogen ion formed from (III) and (IV) respectively.

FIG. 4. FIG. 5.

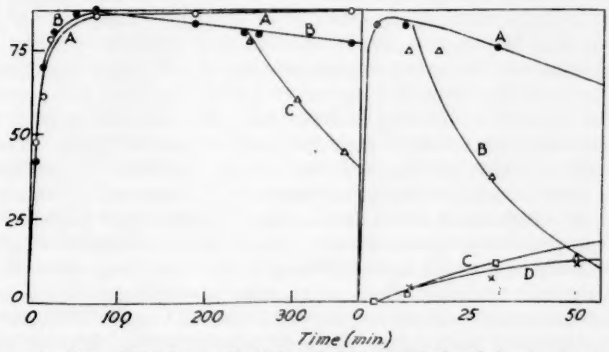


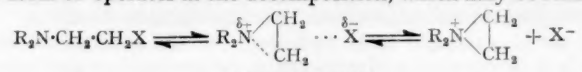
FIG. 4. *Decomposition of* N-2-*bromoethyl*-N-*methyl*-1′-*naphthylmethylamine in aqueous acetone.*
A, Bromide ion formed and, *B*, ethyleneiminium ion produced, at 0°. *C*, Decomposition of ethyleneiminium ion at 30°.

FIG. 5. *Effect of* N-2-*hydroxyethyl*-N-*methyl*-1′-*naphthylmethylamine* (V) *on decomposition of* N-2-*bromoethyl*-N-*methyl*-1′-*naphthylmethylamine* (*curve B*).
A, Normal decomposition. *D* and *C*, Formation of hydrogen ion with and without added (V) respectively.

phonates, so that we regard this, with slight reserve, as providing confirmation of the formation of ethyleneiminium ions.

The primary decomposition process in reactions of this type has been formulated as conforming to the unimolecular mechanism of aliphatic substitution (Hanby, Hartley, Powell, and Rydon, *loc. cit.*; Ross, *J.*, 1949, 183) but this is improbable. Substituents releasing electrons powerfully to the seat of substitution would be necessary if a primary alkyl bromide were to undergo a rate-determining ionisation: the alkylarylalkylamino-group lacks such electron-releasing powers in saturated systems. Moreover, the observed rates of decomposition of the bromo- and iodo-compounds we have examined are much larger than would be expected for the S_N1 process. It is much more likely that these

reactions pursue an internal bimolecular mechanism wherein the electron-availability at the β-nitrogen atom co-operates in the decomposition, which may be formulated :



(Transition state)

The S_N1 and " internal S_N2 " processes both correspond to first-order kinetics, of course. Approximate values for the basic dissociation constants at 25° of the pharmacologically active members of the series have been determined by measuring the pH of solutions of their salts of known concentration. The values for all the bromo- and iodo-compounds lie between 2×10^{-10} and 3×10^{-11}, but the chloro-compounds have values between 3×10^{-7} and 10^{-8}, so it appears that the strength of the carbon–halogen bond is the major feature in determining rates of cyclisation.

Nickerson and Gump (*loc. cit.*) surveyed the relation between chemical structure and antiadrenaline activity in a large group of *N*-substituted 2-halogenoethylamines and concluded that the derived ethyleneiminium ion is the pharmacologically active species. The present investigation and the related pharmacological one (Graham and Lewis, *loc. cit.*) provide the first explicit evidence in favour of this conclusion. Points determined by biological assay, using both antiadrenaline and antihistamine activity, at appropriate times, of solutions prepared exactly as for the kinetic experiments, lie close to the chemically determined curves recording the life-histories of the substituted ethyleneiminium ions. This close correspondence has been demonstrated for three *N*-ethyl-*N*-2-halogenoethyl-1′-naphthylmethylamines in which the halogen is chlorine, bromine, or iodine. It seems very probable not only that ethyleneiminium ions are formed when these halogenoethylamines are liberated from their salts, but also that these ions are the pharmacologically active species.

Nickerson also suggested that the influence of structure of the ion on pharmacological activity, with special reference to the *N*-substituents, is due to varying ionic stabilities arising from resonance. The greatest pharmacological activity is undoubtedly associated with *N*-substituents of the type $ArCH_2\cdot$ or $Ar\cdot O\cdot CH_2\cdot CH_2\cdot$, but the possible influence of structure on the stability of the ethyleneiminium ions formed is far from clear, especially if an attempt is made to write down the appropriate canonical forms. Both the ethyleneimine and the ethyleneiminium ring will bear strong structural resemblance to the *cyclo*propane ring. If we accept the structure proposed by Cromwell (*J. Org. Chem.*, 1952, **17**, 414) for the ethyleneimine ring, based on that due to Coulson and Moffitt (*Phil. Mag.*, 1949, **40**, 1) for *cyclo*propane, then the character of the partially delocalised bonds in the three-membered ring leads to a ready understanding of the stabilising influence of substituents on C or N with p or π orbitals. There is, however, no evidence that substituents of this type promote antiadrenaline activity. We think that this aspect of Nickerson and Gump's structural speculations is premature. Even within the limited field we have investigated there are anomalies, as the Table shows, for *N*-2-chloroethyl-*N*-methyl-2′-naphthylmethylamine, administered as its hydrochloride, is inactive against adrenaline, but yields ethyleneiminium ions *in vitro*; nor is there any clear relation between the maximum proportion of ethyleneiminium ion formed and antiadrenaline activity of the halogeno-amine salts. In our compounds the importance of the formation of the substituted ethyleneiminium ion for antiadrenaline and antihistamine activity is established, but the origin of the influence of the structure of the *N*-substituents on pharmacological activity requires further investigation.

Under our conditions dibenamine $[N(CH_2Ph)_2\cdot CH_2\cdot CH_2Cl,HCl]$ lost covalent chlorine extremely slowly and no thiosulphate-consuming species was detectable, but in the presence of an excess of thiosulphate, dibenamine, or a transformation product thereof, reacted slowly with thiosulphate. Harvey and Nickerson (*J. Pharmacol.*, 1953, **109**, 328) have, however, observed different behaviour in **7** : 3 ethanol–water at 27°.

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THE UNIVERSITY, SOUTHAMPTON. [*Received, January 9th*, 1954.]

Nucleophilic Displacement Reactions in Aromatic Systems. Part IV. Kinetics of the Reactions of* o- *and* p-*Halogenonitrobenzenes with Piperidine and with Morpholine.*

By N. B. Chapman, R. E. Parker, and P. W. Soanes.

[Reprint Order No. 5033.]

Arrhenius parameters have been determined for the second-order reactions in ethanol of all the *o*- and *p*-halogenonitrobenzenes with piperidine, and for the reactions of the fluoro- and bromo-compounds with morpholine. The reactions of the fluoro-compounds obey a rate law, $dx/dt = k(b-x)(a-nx)$ where $1<n<2$, and a method for determining k is developed. It is shown that a possible concurrent ethanolysis of the halogeno-compounds is of little importance and does not vitiate the results. For *para*-compounds the order of reactivity, $F \gg Cl \sim Br > I$, is shown to be mainly due to a diminution in E for the fluoro-compound of ~ 4 kcal. which, as solvation of the transition state of the reactions of this fluoro-compound is not apparently accentuated, is ascribed to diminished repulsion energy in formation of the transition state. The behaviour of the other *para*-compounds is also briefly discussed. The reactions of the *ortho*- are faster than those of the *para*-compounds at all temperatures at which the reactions have significant speed. Only a tentative discussion of the Arrhenius parameters is possible.

Although the kinetics of the reactions of *o*- and *p*-halogenonitrobenzenes with amines have been studied previously, *e.g.* by Holleman, de Mooy, and ter Weel (*Rec. Trav. chim.*, 1915, **35**, 1), and by Miller *et al.*, (*J.*, 1952, 3550; 1953, 1475), there had been no systematic investigation over the whole range of *o*- and *p*-halogenomononitrobenzenes when this investigation was begun in 1949. A preliminary account of this work has appeared (*Chem. and Ind.*, 1951, 148). Brieux and Deulofeu (*ibid.*, 1951, p. 971; *Anal. Asoc. Quím. Argentina*, 1951, **39**, 189) reported the results of a kinetic investigation of similar reactions with piperidine in benzene, but they did not investigate the reactions of the fluoro-compounds. The present paper records an investigation of the reactions in ethanol of all the *o*- and *p*-halogenonitrobenzenes with piperidine and of some with morpholine under conditions such that the order of reaction can be established. Several investigations of the solvolysis by piperidine of some of the compounds studied are on record (*e.g.* Berliner and Monack, *J. Amer. Chem. Soc.*, 1952, **74**, 1574). Non-kinetic quantitative investigations (*e.g.* Franzen and Bockhacker, *Ber.*, 1920, **53**, 1174; Brewin and Turner, *J.*, 1928, 332) are also available. The kinetics of the reactions in ethanol of *p*-halogenonitrobenzenes with ethoxide ions have recently been investigated by Bevan (*J.*, 1951, 2340), and the field has been reviewed by Bunnett and Zahler (*Chem. Reviews*, 1951, **49**, 273). The present investigation provides Arrhenius parameters for all the reactions in question, with a view to elucidation first of the influence of the halogen on reactivity and, secondly, of the fact that the rates of the reactions of the *ortho*-compounds with amines are greater than those for the *para*-compounds in the ranges of temperature so far investigated.

Experimental

Materials.—*o*- and *p*-Chloro- and -bromo-nitrobenzene and *p*-iodonitrobenzene (from British Drug Houses, Ltd.) were recrystallised from ethanol to constant m. p.; or from 1 : 1 aqueous nitric acid (Brand, *J.*, 1950, 1000) and then from ethanol. The different samples showed no significant differences in kinetic experiments. *o*-Iodonitrobenzene was prepared from *o*-nitroaniline and recrystallised from light petroleum (b. p. 60—80°). *p*-Fluoronitrobenzene was prepared by Bradlow and VanderWerf's method (*J. Amer. Chem. Soc.*, 1948, **70**, 654), fractionated at 15 mm. (50 × 1·5 cm. column packed with Fenske helices), and crystallised from ethanol between room temperature and $\sim -80°$ to a constant m. p. of 26·7—28·0°. *o*-Fluoronitrobenzene was prepared by Swarts's method (*Bull. Acad. roy. Belg.*, 1914, 178), being separated from the *p*-isomer by repeated fractional distillation (60 × 1·5 cm. column, Fenske helices),

* Part III, *J.*, 1954, 1190.

and had m. p. −5·8° to −5·5°, b. p. 221·6—221·7°/760 mm. (corr.), d_4^{16} 1·3382, d_4^{3} 1·3227, n_D^{14} 1·5349, and n_D^{20} 1·5321.

Amines.—Piperidine and morpholine were purified as described in Part III (*loc. cit.*) and had b. p. 106·4/760 mm., n_D^{20} 1·4532, and b. p. 128·0°/760 mm., n_D^{20} 1·4549, respectively.

Solvent.—This was prepared as described in Part I (*J.*, 1952, 437).

Reaction Products.—The *N-o*-nitrophenyl and *N-p*-nitrophenyl derivatives of piperidine and morpholine were isolated from solutions used in kinetic experiments and had m. p.s in agreement with those in the literature. The very hygroscopic *piperidine hydrofluoride* was prepared by Neusser's method (*Z. anorg. Chem.*, 1940, **244**, 13), the crude solid product being crystallised from benzene, and the material carefully protected from the atmosphere during all operations (Found: $C_5H_{11}N$, 79·3; F, 17·4. $C_5H_{11}N,HF$ requires $C_5H_{11}N$, 81·0; F, 18·1%). As the product decomposed on desiccation at 15 mm., no effort was made to purify it further. The low analytical figures are probably due to adhering benzene. *Morpholine hydrofluoride monohydrate*, a deliquescent crystalline solid, was similarly prepared and crystallised from benzene containing a little ethanol (Found: C_4H_9ON, 69·7; F, 15·1. C_4H_9ON,HF,H_2O requires C_4H_9ON, 69·6; F, 15·2%).

Procedure.—For the fluoro-compounds sealed bulbs were used for the slower reactions: for the faster reactions stoppered calibrated flasks were used. The reaction was arrested by adding the reaction mixture to 20 c.c. of 1 : 1 or (for *ortho*-compounds) 1 : 7 hydrochloric acid and extracting unchanged fluoro-compound with benzene. After the solution had been made strongly alkaline and a little sodium dithionite added to destroy *N-o-* or *-p*-nitrophenylpiperidine, which are steam-volatile and interfere with the final titration, the solution was steam-distilled (100—150 c.c. of distillate for piperidine, 300 c.c. for morpholine) and the unchanged piperidine or morpholine in the distillate was determined acidimetrically (bromophenol-blue). The time of the first analysis was taken as zero, thus eliminating initial errors. Blank determinations showed that this procedure was satisfactory for piperidine and morpholine under the reaction conditions. For the other halogeno-compounds the method of sealed bulbs was used, and, as the reactions were carried out at 70—90°, cooling and addition of dilute sulphuric acid adequately arrested the reaction. Halide ions were determined potentiometrically in the diluted solution with a silver indicator electrode and a lead amalgam–lead sulphate (in saturated magnesium sulphate solution) half-cell. When 0·08N-silver nitrate was used, potential increases of 10, 2·5, and 0·7 v/ml. were obtained at the end-point for iodides, bromides, and chlorides respectively. E.M.F. readings were stable to 2 mv. some 5 sec. after addition of reagent (cf. Edwards, *Trans. Faraday Soc.*, 1937, **33**, 1294); it was desirable to shield the titration cell from direct light. Blank experiments showed that none of the other substances present in kinetic experiments vitiated the determination of halogens by this method.

Results

Detailed values for some of the reactions are given in Table 1, and all the results are summarised in Table 2.

For the reactions of all save the fluoro-compounds, it was confirmed that two moles of amine are consumed per mole of halogeno-compound, since, for example, piperidine hydrobromide reacted negligibly slowly with *o*- and *p*-bromonitrobenzene in ethanol at 90°, and for the reaction of *p*-bromonitrobenzene with piperidine in ethanol at 90° piperidine determinations gave the same rate coefficients as bromide-ion determinations. Thus

$$k = \frac{1}{2t(0{\cdot}5a - b)} \cdot 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

Halide determinations at " infinite " time (at least thirty times the half-life of the reaction) gave values of 99·7—100·2% reaction for the *ortho*-compounds. For the *para*-compounds the value was 98·7—99·7%. We ascribe this deficit to the intervention of a reductive side reaction. From these observations we conclude that reversibility of the reactions may be neglected and that the reagents and analytical procedure were satisfactory. The reactions were shown to be of the second order within experimental error by the half-life method.

For the fluoro-compounds the stoicheiometry of the reactions is more complicated. The amine hydrofluorides react more or less rapidly under the conditions employed in kinetic experiments with the fluoronitrobenzenes. However the same rate law as above was used for calculation of the velocity coefficients, subject to considerations explained on p. 2111. Determinations at infinite time showed 100 ± 1·5% reaction. The order of the reactions was determined by the differential method (Laidler, " Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14).

TABLE 1.

Reactions of Piperidine.

p-*Fluoronitrobenzene at* 40·0°. $a = 0{\cdot}3867$M, $b = 0{\cdot}0956$M.*

Time (min.)	81	156·5	301	425	553	1216	∞
Decompn. (%)	16·4	28·8	47·4	57·9	65·8	86·7	99·1
10^5k	9·67	9·86	10·35	10·30	10·20	9·93	—

Mean $k = 10{\cdot}05 \pm 0{\cdot}23 \times 10^{-5}$ *; after correction for solvent expansion, $10{\cdot}33 \pm 0{\cdot}24 \times 10^{-5}$. Order with respect to amine 1·06; with respect to *p*-fluoronitrobenzene 1·00.

o-*Bromonitrobenzene at* 79·7°. $a = 0{\cdot}4$M, $b = 0{\cdot}1$M.

Time (hr.)	4·22	6·93	14·55	19·63	27·02	45·20	62·50	92·33
Decompn. (%)	13·4	20·7	37·6	45·9	55·5	71·7	80·2	89·7
10^5k	2·45	2·44	2·49	2·48	2·47	2·49	2·44	2·50

Mean $k = 2{\cdot}64 \pm 0{\cdot}02 \times 10^{-5}$ after correction for solvent expansion.

p-*Bromonitrobenzene at* 79·9°. $a = 0{\cdot}4$M, $b = 0{\cdot}1$M.

Time (hr.)	15·97	25·00	47·33	64·42	88·42	113·23	145·37	184·6	304·7
Decompn. (%)	13·8	20·8	35·6	44·4	54·3	62·3	70·2	76·8	89·2
10^6k	6·70	6·85	7·15	7·23	7·32	7·39	7·45	7·36	7·49

Mean $k = 7{\cdot}22 \pm 0{\cdot}21 \times 10^{-6}$. After extrapolation to zero time (see p. 2112) and correction for solvent expansion $k = 6{\cdot}96 \times 10^{-6}$.

Reactions of Morpholine.

o-*Fluoronitrobenzene at* 40·0°. $a = 0{\cdot}3929$M, $b = 0{\cdot}0968$M.

Time (min.)	200·5	420·5	661	1403	1910	∞
Decompn. (%)	21·4	39·8	52·5	74·0	83·9	99·9
10^5k	5·25	5·60	5·47	5·18	5·52	—

Mean $k = 5{\cdot}40 \pm 0{\cdot}15 \times 10^{-5}$; after correction for solvent expansion $5{\cdot}55 \pm 0{\cdot}15 \times 10^{-5}$. Order with respect to amine 1·02, with respect to *o*-fluoronitrobenzene 1·06.

o-*Bromonitrobenzene at* 90·6°. $a = 0{\cdot}4176$M, $b = 0{\cdot}2012$M.

Time (hr.)	7·45	17·00	32·47	45·17	83·17	145·17	212·50
Decompn. (%)	10·3	21·2	35·5	44·6	63·7	80·1	89·0
10^6k	9·99	9·85	9·90	9·89	9·99	9·98	9·96

Mean $k = 9{\cdot}94 \pm 0{\cdot}05 \times 10^{-6}$; after correction for solvent expansion $10{\cdot}74 \pm 0{\cdot}06 \times 10^{-6}$.

p-*Bromonitrobenzene at* 90·0°. $a = 0{\cdot}4170$M, $b = 0{\cdot}2034$M.

Time (hr.)	32·33	61·62	94·87	144·0	211·6	331·9	412·1	662·5
Decompn. (%)	12·5	22·1	31·5	43·1	55·2	70·0	76·4	88·3
10^6k	2·84	2·87	2·90	2·96	3·00	3·07	3·08	3·10

Mean $k = 2{\cdot}98 \pm 0{\cdot}09 \times 10^{-6}$; after extrapolation to zero time and correction for solvent expansion $k = 3{\cdot}00 \pm 0{\cdot}09 \times 10^{-6}$.

* a is the initial amine concentration and b that of the halogeno-compound. All values of k, the velocity coefficient, are in l. mole^{-1} sec.$^{-1}$

TABLE 2.

Nitrobenzene derivative	Amine	10^6k 70·0°	80·0°	90·0°	E (kcal. mole^{-1})	$\log_{10} A$
o-Fluoro- *	Piperidine	108	252	536	14·8	7·0
	Morpholine	12·3	27·4	55·4	13·8	5·4
o-Chloro-	Piperidine	6·86	14·7	29·8	18·1	6·4
o-Bromo-	Piperidine	12·8	27·0	56·0	18·3	6·8
	Morpholine	2·48	5·17	10·3	17·7	5·6
o-Iodo-	Piperidine	5·00	11·0	23·2	19·2	6·9
p-Fluoro- *	Piperidine	24·7	50·8	105	13·2	5·3
	Morpholine	2·22	4·57	9·11	12·9	4·0
p-Chloro-	Piperidine	2·64	5·55	10·8	17·1	5·3
p-Bromo-	Piperidine	3·59	7·10	13·9	16·8	5·2
	Morpholine	0·63	1·30	2·57	17·7	5·1
p-Iodo-	Piperidine	—	—	4·0	18·0	5·5

k's are accurate to ± 3%. Usually some 80—90% of the reaction was studied. E's are accurate to ± 0·5 kcal. mole^{-1}, and values of $\log_{10} A$ to ± 0·5 unit. * 50° lower.

DISCUSSION

The stoicheiometry of the reactions of the fluoro-compounds corresponds to a rate law $dx/dt = k(b - x)(a - nx)$ where $1<n<2$. The necessary correction, which will be greater for the weaker base, to k calculated with $n = 2$ may be determined as follows. From experiments with morpholine k is determined by assuming $n = 2$, and from the slope of

x–t curves for experiments with morpholine hydrofluoride, and $(b - x)$ at time t, and the approximate value of k, a value of [free morpholine] is obtained. From this and other experimentally determined magnitudes the equilibrium constant K for the dissociation of morpholine hydrofluoride is determined. K is then used to correct the value of the morpholine concentration in the expression $dx/dt = k$[fluoro-compound][morpholine] for reactions of morpholine itself, whence a corrected value of k is obtained by determining dx/dt from the slope of an appropriate x—t curve. If necessary k may be obtained more exactly by repeating the process. However, the maximum correction to k that we have determined is $\sim 2\%$ so that we have neglected this correction throughout and determined k's by using the above rate law with $n = 2$. For reactions of piperidine the correction is $\sim 0{\cdot}1\%$.

In these reactions, of all those so far studied, the intervention of ethanolysis (cf. Part II, *J.*, 1953, 3394) is the most acute. However, the value of the relative rate of ethanolysis at $x\%$ " apparent reaction ", α_x, may be evaluated from the relation $\alpha_x = \{c[R_2H_2N^+]\}^{-1}$, where $c = k_4/k_2K_b$ (cf. Part II, p. 3394, and *Chem. and Ind.*, 1953, 1266). For the reaction of *p*-chloronitrobenzene with piperidine at 90°, where α_x is largest, the use of Bevan's value of k_2 (*J.*, 1951, 2340) gives $\alpha_x = 0{\cdot}1x^{-1}$. The correction to be applied to the mean rate coefficient will nevertheless be only $\sim 3\%$, since after $\sim 30\%$ reaction α_x is negligible. Such corrections have not been applied to the values in Table 2, as they are of the same order as the experimental error, but the slight reduction of the k's should be borne in mind in what follows. As morpholine is a weaker base than piperidine by a factor of $\sim 10^3$ in water at 25°, it is probable that corrections for ethanolysis are unimportant for its reactions.

The reactions of the *para*-compounds, fluorides excepted, show velocity coefficients with a steady upward trend as the reaction proceeds, so these have been extrapolated to values for zero time. This observation is probably due to a salt effect of the products, but is in any case only of minor importance. The Arrhenius parameters for the reaction of *p*-iodonitrobenzene with piperidine are subject to considerably greater errors than the remainder owing to experimental factors, particularly the low solubility of the iodo-compound and the slowness of the reactions at 90° and 118°. At the higher temperature k is reliable to $\pm$ 10% only.

TABLE 3.

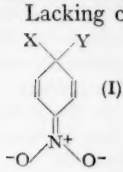
Nitrobenzene derivative	Reactions of piperidine in ethanol			Reactions of piperidine in benzene [1]			Reactions of ethoxide ions in ethanol		
	$\log_{10} A$	E (kcal. mole^{-1})	10^5k at 90°	$\log_{10} A$	E (kcal. mole^{-1})	10^5k at 90°	$\log_{10} A$	E (kcal. mole^{-1})	10^5k at 90°
o-Fluoro- ...	7·0	14·8	1230	—	—	—	11·7 [3]	20·1	4×10^4
o-Chloro- ...	6·4	18·1	2·98	3·8	13·4	5·4	10·0 [4]	22·2	39·7
o-Bromo- ...	6·8	18·3	5·60	4·6	14·1	13·9 [5]	—	—	—
o-Iodo- ...	6·9	19·2	2·32	5·0	15·3	6·2	—	—	—
p-Fluoro- ...	5·3	13·2	225	—	—	—	10·7 [2]	19·0	$2{\cdot}2 \times 10^4$
p-Chloro- ...	5·3	17·1	1·08	2·3	13·7	0·11	9·0 [2]	20·1	96·3
p-Bromo- ...	5·2	16·8	1·39	3·6 [5]	15·5 [5]	0·20 [5]	9·2 [2]	20·3	83·8
				2·6	13·6	0·26			
p-Iodo- ...	5·5	18·0	0·40	5·8	19·5	0·12	—	—	7·1 [2]

[1] Brieux and Deulofeu, *loc. cit.* [2] Bevan, *loc. cit.* [3] Bevan, *J.*, 1953, 655. [4] Riklis, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1511. [5] P. W. Soanes, unpublished work.

In Table 3 are assembled velocity coefficients and Arrhenius parameters determined by us (ethanol) and by Brieux and Deulofeu (benzene) for reactions of piperidine, and those in the literature for ethoxide-ion reactions. We have independently confirmed Brieux and Deulofeu's values for the reaction of *o*-bromonitrobenzene, but have obtained different values for that of the *p*-isomer (Chapman and Soanes, unpublished work). Edwards (*loc. cit.*) has drawn attention to the complications attending Menschutkin-type reactions in non-polar solvents, where the salts formed are insoluble. Despite the insolubility of piperidine salts in benzene, we have observed regular kinetics as, apparently, have Brieux and Deulofeu. Nevertheless, the phenomena discussed by Edwards could only be neglected if the results of experiments having widely varied initial concentrations were available. Therefore we merely point out that when one passes from ethanol to benzene as solvent the trend in Arrhenius parameters is of the same kind as that shown by various reactions

of amines and aliphatic halides (cf. Moelwyn-Hughes, " Kinetics of Reactions in Solution," Oxford, 1947, pp. 205 *et seq.*).

Lacking compelling evidence of the intervention of stable intermediate complexes in these reactions, we assume as before a simple bimolecular mechanism (cf. Brady and Cropper, *J.*, 1950, 507, and Miller *et al.*, *loc. cit.*). While accepting in part the criticism advanced by Bunnett and Zahler (*loc. cit.*, p. 298) of previous formulations of the transition state, we believe that formula (I) represents for *para*-compounds an extreme configuration towards which the transition state tends rather than the actual transition state of the bimolecular substitution we assume to occur.


(I)

Two points are noteworthy for the reactions of the *para*-compounds with piperidine in ethanol: the approximate constancy of entropy of activation, and the freedom from steric complications. There appears to be no significant accentuation of solvation of the transition state for the fluoro-compound in this series, and our previous analysis of a similar problem (Chapman and Parker, *loc. cit.*) may have over-emphasised solvation to the neglect of other factors. Of the factors thought to determine energy of activation (cf. Glasstone, Laidler, and Eyring, " Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 141), the strength of the bond formed is constant throughout this series. The major variables are the strength of the bond broken and the repulsion energy. Miller *et al.* (*loc. cit.*) have dealt with a similar problem in a crudely quantitative way in terms of the difference in bond strengths and the difference in ionic resonance energies between ArX and ArI. Although they do not make it clear, it appears to us that the basis of their treatment is the assumption that differences of ionic resonance energies, taken as measuring differences in the polarity of carbon–halogen bonds, roughly measure the differences of repulsion energy themselves largely determined by the charge at the seat of substitution. Our view is that such assumptions limit the analysis of the problem to the qualitative. If we assume that the total electron-withdrawal effect of halogen at the seat of substitution is in the order F>Cl>Br>I, the repulsion energy will increase in the reverse order. Provided the transition state tends closely towards the quinonoid structure (I) the strengths of the bonds broken will probably be less important because these bonds will be little stretched in attaining the transition state, so that the order of repulsion energies determines the important features of the observed order of energies of activation. However this order, F≪Cl∼Br<I, can only be reproduced in detail by taking account also of the variation in bond strengths. The primary condition for nucleophilic aromatic substitution is appropriate distortion of the delocalised π-orbital by, for example, a nitro-group. The inductive effects of halogens are, on the whole, unimportant by comparison.

Reactions of the *ortho* compounds are more complex sterically. Toussaint (*Mem. Soc. Roy. Soc. Liége*, 1952 **12**, 5) has examined *o*-chloronitrobenzene by *X*-ray analysis, and in a personal communication states that " if it is assumed that the nitro-group is not deformed but simply rotated about the C–N bond, the angle of rotation would be at least 30°." If a planar configuration is assumed, the overlap between the nearer oxygen atom of the nitro-group and the halogen atom may be determined. These and similar overlaps for the transition state based on a tetrahedral model of the seat of substitution have been determined by Beckwith, Miller, and Leahy (*loc. cit.*) and by us using a coplanar fully *o*-quinonoid model of the transition state. Only qualitative conclusions may be drawn from these geometrical results because of the assumptions involved, as follows. When the reagent is small, formation of the transition state for these reactions will, on the above hypothesis, allow the nitro-group to become coplanar with the ring with diminished overlap between the nearer oxygen atom of the nitro-group and halogen in every case, the diminution being in the order F<Cl<Br<I. With a more bulky reagent it is probable that the total overlaps, including those between the nitro-oxygen atoms and atoms of the reagent, will not be much reduced. This point is difficult to determine geometrically because the position of the reagent, *e.g.*, piperidine, in the transition state is not accurately known. To compare two different reagents of similar geometry assumptions may be made with more confidence (cf. Part I, p. 444). Because of large variations in A and the complexity of the problem, the basis of the influence of halogen variation on E for these reactions remains obscure.

The increases in E observed on passing from *p*- to *o*-halogenonitrobenzenes may arise from a " net *ortho*-effect " (cf. Part I, p. 445) weakened solvation, and a relatively weak tautomeric effect of the nitro-group when in the *ortho*-position, tempered by a more powerful inductive effect and a small decrease in steric inhibition of resonance in the transition state for the *ortho*-compounds. The corresponding increase in A is probably due in part to diminished solvation, possibly because of congestion near the polar centres in the transition state for the *ortho*-compounds. The ultimate effect is that E for the *ortho*-compounds is some 1000—1500 cal. greater than for the *para*-compounds, but this is always offset by such an increase in A as to ensure faster reactions for the *ortho*-compounds.

It is noteworthy that, with piperidine and morpholine as reagents, *o*-halogenonitrobenzenes react faster than the corresponding *para*-compounds at all temperatures at which the reactions proceed with significant speed. The same is true for *o*- and *p*-fluoronitrobenzenes reacting with ethoxide ions in ethanol, but the reverse is true for *o*- and *p*-chloronitrobenzenes (cf. Table 3). Finally we may add that the reactions of morpholine reported here conform to the same broad pattern as those of piperidine.

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THE UNIVERSITY, SOUTHAMPTON. [*Received, January 16th,* 1954.]

A Quantitative Study of the Autoxidation Products of Elaidic Acid.

By GEORGE KING.

[Reprint Order No. 5053.]

Elaidic acid has been oxidised with gaseous oxygen at 47° and at 78°, with and without a cobalt catalyst. Confirmatory evidence has been obtained for the formation of ketol derivatives, and formic acid has been identified among the volatile autoxidation products. Methods of estimating ketol and other carbonyl compounds have been developed, and the course of oxidation has been followed by the systematic quantitative analysis of the products.

QUANTITATIVE data concerning autoxidised oleic and elaidic acids are peculiarly fragmentary, a fact which may be attributed largely to uncertainty regarding the qualitative composition of these products, no less than to their complexity, most authors having confined their attention to the uptake of oxygen and changes of peroxide content, supplemented by estimations of molecular and equivalent weights, and iodine and saponification values.

Ellis (*Biochem. J.*, 1936, **30**, 753) showed that elaidic acid oxide is a major product of the autoxidation of either elaidic or oleic acid. More recently (*ibid.*, 1950, **46**, 129; *J.*, 1950, 9) he obtained evidence of the formation of unsaturated keto-acids in significant amounts and established the presence of acyl esters of dihydroxystearic acid, more especially among the products obtained from elaidic acid above 60°. According to this author, the keto-acids are of three types, of which the first two predominate in oxidations conducted at relatively low temperatures (*ca.* 50°): first, γ- (I) and κ-keto-acids (II) in which the carbonyl group is conjugated with the ethylenic linkage; second, polymers, possibly cyclic dimers, *e.g.*, (IV), which resist alkaline hydrolysis; third, other (possibly β-)keto-acids which give enol reactions and yield carbon dioxide on hydrolysis. Acids of the first type yield nonaldehyde and nonan-2-one almost quantitatively on hydrolysis; they also absorb ultra-violet light strongly and selectively in the region of 224 mμ, a property which affords an alternative basis for their estimation (King, *J.*, 1951, 1980).

The free 9 : 10-ketol derivatives of stearic acid have never been isolated from autoxidised oleic or elaidic acid, although evidence has been adduced for ketol formation during the autoxidation of unsaturated fatty acids and their glycerides or simple esters (Ellis, *J. Soc. Chem. Ind.*, 1926, **45**, 193T; Morrell and Marks, *J. Oil Colour Chem. Assoc.*, 1927, **10**, 193; 1929, **12**, 183; Skellon, *J.*, 1948, 343). The reduction of Fehling's solution is not in itself a

reliable indication of α-ketol groups, since this may be due to various fission products, such as azelaic semialdehyde, or to α-unsaturated carbonyl compounds. The present work, however, confirms α-ketol formation from elaidic acid, particularly during the advanced stages of autoxidation, since (*a*) it is then possible to derive a bis-2 : 4-dinitrophenylhydrazone, similar to, if not identical with, that prepared from the 9 : 10-ketol

FIGURES 1—4. *Autoxidation of elaidic acid.*

FIG. 1.

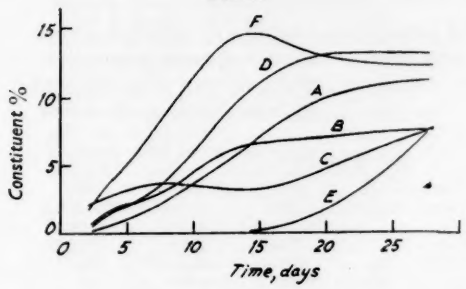


FIG. 2.

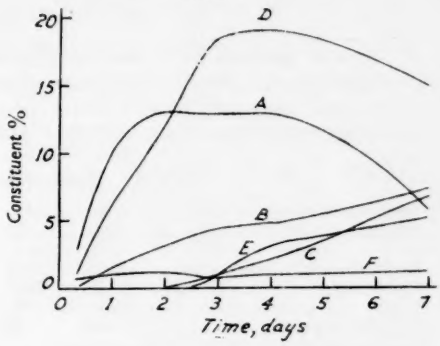


FIG. 3.

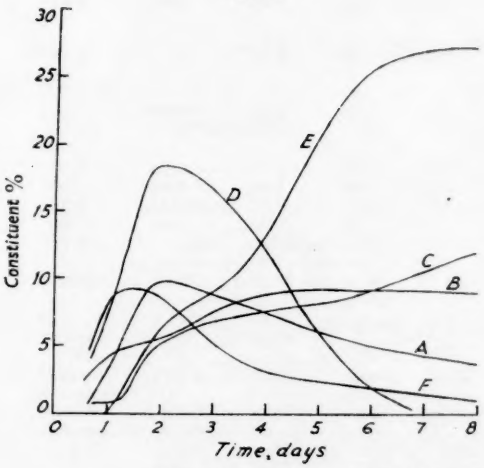
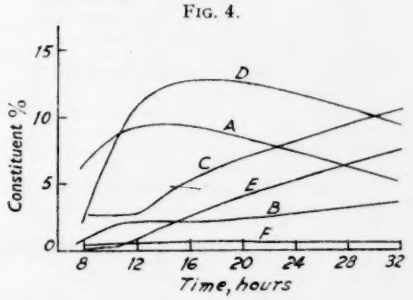


FIG. 4.



Percentages refer to the total non-gaseous oxidation products (as 100%).

FIG. 1. *At 47°, without catalyst.*
FIG. 2. *At 47°, with 0·5% of cobalt.*
FIG. 3. *At 78°, without catalyst.*
FIG. 4. *At 78°, with 0·5% of cobalt.*

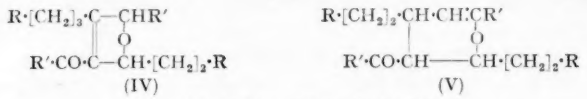
A, η- and κ-Oxoelaidic acids.
B, Ketol from stearic acid.
C, Other oxo-acids, as $C_{18}H_{32}O_3$.
D, Elaidic acid oxide.
E, Dihydroxystearic acid (combined).
F, Hydroperoxyelaidic acid.

derivatives of stearic acid (King, *J.*, 1936, 1791), and (*b*) distillation of the product with periodate affords nonaldehyde, which, in the absence of free dihydroxystearic acid, indicates the presence of a 10-hydroxy-9-oxo-derivative.

The steam-volatile nonanoic and octanoic acids and the water-soluble azelaic and suberic acids, together with carbon dioxide, have long been recognised among the products of oxidative cleavage of elaidic acid (Ellis, *Biochem. J.*, 1936, **30**, 753). It is now shown that small amounts of formic acid are also formed, especially at higher temperatures.

This acid has already been observed by O'Neill during the autoxidation of linseed-oil films (see Bawn, *Nature*, 1953, **171**, 1059).

$R{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}COR'$ (I) $\quad R{\cdot}CH_2{\cdot}CO{\cdot}CH{:}CH{\cdot}CH_2R'$ (II) $\quad R{\cdot}CO{\cdot}CH{:}CH{\cdot}[CH_2]_2{\cdot}R'$ (III)



(IV) (V)

($R = CH_3{\cdot}[CH_2]_5$; $R' = [CH_2]_6{\cdot}CO_2H$)

Suitable methods have also been devised for estimating α-ketol and carbonyl groups (see Experimental section), and these, coupled with existing methods of estimating oxiran-oxygen and other data, have enabled the course of oxidation of elaidic acid to be followed in much greater detail than hitherto (Tables 1—9; Figs. 1—4), thus revealing, *inter alia*,

TABLE 1. *Autoxidation at 47° without a catalyst.*

Time (days)	2	4	7	14	21	28
Physical condition	Cryst.	Cryst.	Cryst.	Oily semi-solid	Semi-solid	Oil, some cryst.
Reduction of Fehling's soln.	None	None	None	Trace	Slight	Slight
Equiv. wt.	283	285	291	299	292	279
I val.	90	87	83	64	45	31
$E^{1\%}_{1\,cm.}$ at 224 mμ	2·0	5·0	11·6	36·1	56·9	62·2
Neutral, steam-volatile oil (mainly nonanal and nonan-2-one) (%)	0·21	0·31	0·64	1·70	2·82	2·41
Volatile oil (nonanal and nonanone) resulting from hydrolysis on distilln. with 0·5N-NaOH (%)	Trace	0·10	0·53	2·07	3·80	4·15
Nonanal on distilln. of the residual solution from the above hydrolysis with KIO_4 at pH 8·0 (%)	0·2	0·2	0·85	1·49	3·60	5·44
Saponification value	0·0	2	18	37	59	80
Nonanal resulting from oxidn. with KIO_4 at pH 8·0 (%)	0·0	0·35	0·48	1·17	1·28	1·35
Carbonyl (%)	0·24	0·57	0·89	1·80	2·64	2·95
Oxiran-O (%)	0·0	0·10	0·17	0·56	0·71	0·70
Active O (%)	0·09	0·21	0·39	0·75	0·64	0·62
Steam-volatile acids, m-equiv. (%)	—	7	10	21	31	47
Non-volatile, water-soluble acids, m-equiv. (%)	—	4	11	34	63	89

TABLE 2. *Autoxidation at 47° in the presence of 0·5% of Co.*

Time (hr.)	8	24	48	72	96	168
Physical condition	Cryst.	Cryst.	Semi-solid	Pasty	Pasty	Viscous, semi-cryst.
Reduction of Fehling's soln.	None	Trace	Slight	Weak	Moderate	Fairly strong
Equiv. wt.	289	282	268	256	243	211
I Val.	86	66	50	39	24	8
$E^{1\%}_{1\,cm.}$ at 224 mμ	18·1	57·6	72·1	71·9	71·6	31·9
Neutral, steam-volatile oil (mainly nonanal and nonan-2-one) (%)	0·0	Trace	0·46	0·57	0·66	0·80
Volatile oil (nonanal and nonanone) resulting from hydrolysis on distilln. with 0·5N-NaOH (%)	1·06	3·51	5·15	4·55	4·45	1·41
Nonanal on distilln. of the residual solution from the above hydrolysis with KIO_4 at pH 8·0 (%)	0·0	0·8	1·74	2·51	3·32	4·41
Saponification value	3	17	34	47	52	81
Nonanal resulting from oxidn. with KIO_4 at pH 8·0 (%)	Trace	0·27	0·56	0·79	0·85	1·33
Carbonyl (%)	0·37	1·18	1·71	1·83	1·99	1·99
Oxiran-O (%)	0·05	0·34	0·65	0·99	1·02	0·79
Active O (%)	0·03	0·05	0·06	0·04	0·05	0·06
Steam-volatile acids, m-equiv. (%)	5	16	26	37	49	61
Non-volatile, water-soluble acids, m-equiv. (%)	3	21	51	68	90	118

TABLE 3. *Autoxidation at 78° without a catalyst.*

Time (hr.)	16	32	48	96	114	192
Physical condition	Cryst.	Slightly sticky	Semi-cryst.	Mainly oil	Mainly oil	Pale yellow oil
Reduction of Fehling's soln.	None	Slight	Weak	Moderate	Fairly strong	Fairly strong
Equiv. wt.	289	298	288	277	273	273
I Val.	82	59	39	14·5	10	10
$E^{1\%}_{1\,cm.}$ at 224 mμ	6·3	32·4	54·4	41·1	28·3	22·1
Neutral, steam-volatile oil (mainly nonanal and nonan-2-one) (%)	0·18	1·50	1·50	0·57	0·55	0·47
Volatile oil (nonanal and nonanone) resulting from hydrolysis on distilln. with 0·5N-NaOH (%)	0·24	1·75	3·31	2·39	1·54	1·17
Nonanal on distilln. of the residual solution from the above hydrolysis with KIO_4 at pH 8·0 (%)	0·41	2·65	4·60	7·91	12·31	12·21
Saponification value	3	33	59	111	148	143
Nonanal resulting from oxidation with KIO_4 at pH 8·0 (%)	0·50	0·87	0·99	1·58	1·64	1·58
Carbonyl (%)	0·45	1·41	2·19	2·31	2·23	2·37
Oxiran-O (%)	0·22	0·62	0·98	0·65	0·10	0·0
Active O (%)	0·25	0·47	0·44	0·15	0·09	0·05
Steam-volatile acids, m-equiv. (%)	19	19	28	45	47	46
Non-volatile, water-soluble acids, m-equiv. (%)	7	41	69	111	128	135

TABLE 4. *Autoxidation at 78° in the presence of 0·5% of Co.*

Time (hr.)	8	12	16	32
Physical condition	Solid	Slightly oily	Mainly oil	Oil
Reduction of Fehling's soln.	Trace	Slight	Weak	Weak
Equiv. wt.	292	281	272	246
I Val.	71	52	38	16
$E^{1\%}_{1\,cm.}$ at 224 mμ	38·2	52·2	52·2	28·7
Neutral, steam-volatile oil (mainly nonanal and nonan-2-one) (%)	0·50	0·81	0·91	0·70
Volatile oil (nonanal and nonanone) resulting from hydrolysis on distilln. with 0·5N-NaOH (%)	2·06	3·21	3·21	1·21
Nonanal on distilln. of the residual solution from the above hydrolysis with KIO_4 at pH 8·0 (%)	1·04	1·94	2·53	4·52
Saponification value	18	31	46	94
Nonanal resulting from oxidn. with KIO_4 at pH 8·0 (%)	0·15	0·40	0·40	0·64
Carbonyl (%)	1·09	1·50	1·74	1·91
Oxiran-O (%)	0·13	0·57	0·68	0·50
Active O (%)	0·04	0·03	0·04	0·03
Steam-volatile acids, m-equiv. (%)	12	20	29	45
Non-volatile, water-soluble acids, m-equiv. (%)	20	36	51	87

TABLE 5. *Composition (%) of products obtained by autoxidation at 47° without a catalyst.*

Time (days)	2	4	7	14	21	28
η- and κ-Oxoelaidic acids, $C_{18}H_{32}O_3$, deduced from (*a*) $E^{1\%}_{1\,cm.}$ val.	0·1	0·7	1·9	6·4	10·3	11·2
η- and κ-Oxoelaidic acids, $C_{18}H_{32}O_3$, deduced from (*b*) hydrolysis products...	Trace	0·3	1·5	5·2	8·8	9·5
9 : 10-Ketol-acids, as $C_{18}H_{34}O_4$	0·0	1·9	2·7	6·5	7·1	7·5
Other oxo-acids, as $C_{18}H_{32}O_3$	2·0	2·9	3·6	2·9	5·1	7·8
Elaidic acid oxide	0·0	1·8	3·2	10·4	13·2	13·1
Hydroperoxyelaidic acid	1·8	4·1	7·6	14·7	12·6	12·2
Combined dihydroxystearic acid (*a*) KIO_4 method	0·0	0·0	0·0	0·0	2·2	7·7
Combined dihydroxystearic acid (*b*) isolated	0·0	0·0	0·0	0·8	2·3	5·6
Steam-volatile acids, as nonanoic	—	1·0	1·5	3·3	5·0	7·4
Non-volatile, water-soluble acids, as azelaic	—	0·4	1·0	3·2	6·0	8·4
Neutral, steam-volatile oil (mainly nonanal and nonanone)	0·2	0·3	0·6	1·7	2·8	2·4
Unchanged elaidic acid (calc.)	96	89	80	49	24	5

TABLE 6. *Autoxidation at 47° in the presence of 0·5% of Co.*

Time (hr.)	8	24	48	72	96	168
η- and κ-Oxoelaidic acids, $C_{18}H_{32}O_3$, deduced from (*a*) $E^{1\%}_{1\,cm.}$ val.	3·0	10·3	13·0	12·9	12·9	5·6
(*b*) hydrolysis products...	3·2	8·2	11·6	10·3	10·1	3·7
9 : 10-Ketol-acids, as $C_{18}H_{34}O_4$	Trace	1·5	3·1	4·4	4·7	7·4
Other oxo-acids, as $C_{18}H_{32}O_3$	Trace	Trace	Trace	1·0	2·1	6·8
Elaidic acid oxide	1·0	6·3	12·1	18·5	19·1	14·8
Hydroperoxyelaidic acid	0·6	1·0	1·2	0·8	1·0	1·2
Combined dihydroxystearic acid (*a*) KIO_4 method ...	0·0	0·0	0·0	1·0	3·1	5·2
(*b*) isolated	0·0	0·0	Trace	0·5	1·3	4·7
Steam-volatile acids, as nonanoic	0·8	2·6	4·1	5·9	7·7	9·7
Non-volatile, water-soluble acids as azelaic	0·3	2·0	4·8	6·4	8·4	11·1
Neutral, steam-volatile oil (mainly nonanal and nonanone)	0·0	Trace	0·5	0·6	0·7	0·8
Unchanged elaidic acid (calc.)	92	63	42	29	11	0

TABLE 7. *Autoxidation at 78° without a catalyst.*

Time (hr.)	16	32	48	96	144	192
η- and κ-Oxoelaidic acids, $C_{18}H_{32}O_3$, deduced from (*a*) $E^{1\%}_{1\,cm.}$ val.	0·9	5·7	9·7	7·3	4·9	3·7
(*b*) hydrolysis products...	0·7	4·5	7·8	5·9	4·0	3·1
9 : 10-Ketol-acids, as $C_{18}H_{34}O_4$	2·8	4·9	5·5	8·8	9·1	8·8
Other oxo-acids, as $C_{18}H_{32}O_3$	0·8	1·4	5·1	7·6	8·9	12·0
Elaidic acid oxide	4·1	11·7	18·3	12·1	1·9	0·0
Hydroperoxyelaidic acid	4·9	9·2	8·6	3·0	1·8	1·0
Combined dihydroxystearic acid (*a*) KIO_4 method ...	0·0	1·9	6·2	13·2	25·5	27·2
(*b*) isolated	0·0	0·9	6·1	19·9	24·5	23·0
Steam-volatile acids, as nonanoic	3·0	3·0	4·4	7·2	7·5	7·3
Non-volatile, water-soluble acids, as azelaic	0·7	3·9	6·5	10·4	12·0	12·7
Neutral, steam-volatile oil (mainly nonanal and nonanone)	0·2	1·5	1·5	0·6	0·5	0·5
Unchanged elaidic acid (calc.)	85	51	22	0	0	0

TABLE 8. *Autoxidation at 78° in the presence of 0·5% of Co.*

Time (hr.)	8	12	16	32
η- and κ-Oxoelaidic acids, $C_{18}H_{32}O_3$, deduced from (*a*) $E^{1\%}_{1\,cm.}$ val.	6·7	9·3	9·3	5·0
(*b*) hydrolysis products ...	5·2	7·6	7·6	3·2
9 : 10-Ketol-acids, as $C_{18}H_{34}O_4$	0·8	2·2	2·2	3·6
Other oxo-acids, as $C_{18}H_{32}O_3$	3·0	2·8	5·1	10·4
Elaidic acid oxide	2·4	10·7	12·7	9·2
Hydroperoxyelaidic acid	0·7	0·7	0·8	0·6
Combined dihydroxystearic acid (*a*) KIO_4 method	0·2	0·8	2·5	7·6
(*b*) isolated	0·0	Trace	0·8	5·8
Steam-volatile acids, as nonanoic	1·9	3·1	4·6	7·1
Non-volatile, water-soluble acids, as azelaic	1·9	3·4	4·8	8·2
Neutral, steam-volatile oil (mainly nonanal and nonanone)	0·5	0·8	0·9	0·7
Unchanged elaidic acid (calc.)	69	46	28	3

TABLE 9. *Gaseous (or vaporised) products per 100 g. of elaidic acid*

	At 47°		At 78°	
	Alone, 28 days	With 0·5% of Co, 7 days	Alone, 8 days	With 0·5% of Co, 32 hr.
CO_2 (g.)	2·3	7·0	5·3	6·2
Formic acid (g.)	0·86	0·57	1·65	0·38

the conditions most favourable to the formation of the η- and κ-keto-acids with a view to their ultimate isolation. Owing to the complexity of the products the calculated compositions (Tables 5—8) are necessarily approximate and somewhat tentative, and certain of the methods and results call for comment.

Small amounts of neutral steam-volatile oil, isolated by distilling a solution of the oxidation products at pH 8·0, were shown to consist essentially of nonaldehyde and nonan-2-one. This oil exceeded 2% of the total non-gaseous products only after prolonged autoxidation of the acid at 47° without a catalyst. It presumably arose from the hydrolytic decomposition of the acids (I) and (II), yet appeared to be substantially preformed, rather than an artefact consequent upon distillation, the analogous acid (III) suffering almost negligible decomposition when similarly distilled.

The unsaturated keto-acids (I) and (II) were estimated both by hydrolysis and by their absorption of ultra-violet light at 224 mμ. The latter gave somewhat higher, and probably more accurate, results on which the graphs (*A*, Figs. 1—4) are based. The magnitude of the discrepancy between the two sets of values and its apparent independence of temperature do not suggest any extensive dimerisation to (IV), as this compound would retain a high absorptive power in the ultra-violet, but dimerisation to (V) cannot be excluded on these grounds. The formation of (I) and (II) proceeded rapidly during the early stages of autoxidation, a maximum concentration being reached simultaneously with, or a little in advance of, that of the epoxide, after which the concentrations of both fell steadily. The highest yield of conjugated olefin-ketonic acids (13%) occurred after elaidic acid had been oxidised in the presence of cobalt at 47° for 2 days.

Ketol formation, although generally slow, was greater than expected (cf. King, *Nature*, 1953, **171**, 566). A maximum of 9% (calculated as the ketol derivative of stearic acid) was obtained by oxidising pure elaidic acid at 78° for 6 days, while prolonged oxidation at 47° gave 7—8%. In the presence of cobalt the ketol concentration was significantly reduced at the higher temperature.

The nature of the " other oxo-acids " has not yet been elucidated. Their formation is clearly favoured by high temperature and prolonged oxidation, the catalyst having little influence on the concentration. It seems reasonable to suppose that they include non-conjugated polymers, such as (V), α- and β-keto-acids (the former of which may be a source of formic acid), azelaic semialdehyde, and possibly other, unidentified oxo-compounds of lower molecular weight.

Epoxides appear to be formed almost as rapidly as the conjugated keto-acids (I) and (II). A maximum concentration of 19% (as elaidic acid oxide) was observed at 47° in the presence of the catalyst, but at 78° 18% was obtained without a catalyst.

Dihydroxystearic acid was not found in the free state, but was estimated by saponification of the autoxidation products, followed by isolation or by distillation with periodate, the latter usually giving somewhat higher values. Monoacyl derivatives of dihydroxystearic acid result from the action of heat on elaidic acid oxide alone or with other carboxylic acids (Nicolet and Poulter, *J. Amer. Chem. Soc.*, 1930, **52**, 1186; Deatherage and Mattill, *Ind. Eng. Chem.*, 1939, **31**, 1425; Ellis, *Biochem. J.*, 1950, **46**, 134), the esters being fairly soluble in light petroleum if the carboxylic acid is monobasic (*e.g.*, nonanoic), sparingly soluble if dibasic (*e.g.*, azelaic). Their formation was found to be slow and relatively insignificant at 47°, but at 78° prolonged autoxidation of pure elaidic acid gave at least 27% of combined dihydroxystearic acid, its rate of formation being comparable with the rate of disappearance of epoxide. The actual concentration of esters in the autoxidation products may well be double that of the dihydroxy-acid (Tables 5—8). The saponification values, however, are far higher than can be accounted for on the supposition that the dihydroxy-acid is present solely as monoacyl esters (for which 0·564% of dihydroxy-acid corresponds to one unit of sap. value); nor can they be explained adequately by assuming that all the keto-acid, other than (I), (II), and ketols, consists of β-oxoelaidic acid and is saponified exclusively in the sense :

$$R{\cdot}CO{\cdot}CH_2{\cdot}CO_2K + KOH \longrightarrow R{\cdot}CO_2K + CH_3{\cdot}CO_2K$$

No acetate has in any case been detected in the saponification products. It seems probable that *di*acyl esters of dihydroxystearic acid are also present, but even so the saponification values exceed those calculated from the available data.

The peroxide value remained very low in catalysed autoxidations, but in the absence of a catalyst a maximum of 14·7% (as hydroperoxyelaidic acid) was observed at 47°, and 9·2% at the higher temperature (cf. Skellon and Thruston, *J.*, 1949, 1626). These maxima appear to be reached at a relatively early stage of oxidation and in advance of those of epoxide and conjugated keto-acids. So far as the present investigation goes, the concentration of peroxides was alone seriously affected by the presence of cobalt; apart from this the catalyst appeared mainly to accelerate the autoxidation some 3—5 times.

A rough estimate of the amount of unchanged elaidic acid was obtained from the iodine value, allowing for the absorption of iodine by the keto- and hydroperoxy-elaidic acids

and assuming the " other oxo-acids " to contain one double bond per carbonyl group. It is clear (Tables 5—8) that the amount of material unaccounted for, which may contain saturated polymeric products, becomes appreciable during catalysed autoxidations and may reach 40% after 32 hr. at 78°.

Similar work on oleic acid is in progress.

Experimental

Method of Autoxidation.—Oxygen, freed from carbon dioxide and moisture, was bubbled at the rate of 60 ml. per minute by way of a sintered-glass filter-stick through elaidic acid (40—50 g.) at constant temperature. Gaseous products were passed through saturated barium hydroxide solution (500 ml. or more) to absorb carbon dioxide and formic acid vapour. Samples (*ca.* 8 g. each) of the autoxidised acid were withdrawn at intervals for analysis, except when gaseous products alone were being estimated. In catalysed oxidations, 0·5% of cobalt in the form of finely powdered cobaltous hydroxide was incorporated with the acid. The elaidic acid used in these experiments had m. p. 44·5°, equiv. 283, I val. 89—90, $E^{1\%}_{1\,cm.}$ at 224 mμ, 1·25—1·5 (2·0 if admixed with catalyst).

Neutral, Steam-volatile Oil (*mainly Nonanal and Nonan-2-one*).—The product (*ca.* 2 g.), dissolved in cold 0·2N-sodium hydroxide (100 ml.) and brought to pH 8·0 with dilute sulphuric acid without delay, was distilled at the rate of about 1 drop per second into the special trap used for the estimation of dihydroxystearic acid (King, *loc. cit.*). Distillation was facilitated by the addition of a small drop of " antifoam A " to prevent excessive frothing and was stopped after collection of 20 ml. of aqueous distillate. The mass of oil in the trap was deduced from its volume, by assuming a mean density of 0·825 and allowing 0·0013 g. for its solubility in 20 ml. of water. The oil gave a 2 : 4-dinitrophenylhydrazone which crystallised from ethanol in orange-yellow needles, m. p. 88—90° (Found : N, 17·4. Calc. for $C_{15}H_{22}O_4N_4$: N, 17·4%) (the dinitrophenylhydrazone of nonanal has m. p. 106°; that of nonan-2-one, 60°).

The all-glass apparatus used for this and succeeding distillations was thoroughly cleaned with chromic–sulphuric acid before each estimation.

η- and κ-Oxoelaidic Acids (I *and* II) (cf. King, *J.*, 1951, 1983).—(a) *By hydrolysis.* After removal of the pre-formed neutral oil as above, the residue in the flask was made approximately 0·5N by addition of 2·5N-sodium hydroxide (20 ml.) and was distilled slowly into the trap, 30 ml. of distillate being collected during 2 hr. The mixture of nonanal and nonan-2-one (mean *d* 0·825) in the trap was measured after standing for 15 min. and its mass calculated with an allowance of 0·0020 g. for its solubility in the aqueous distillate. The corresponding amount of keto-acids (I and II) was then found by reference to a graph constructed from the following data, which assume that these acids give the same molar percentage of volatile hydrolysis products as the analogous *trans*-11-oxoheptadec-9-ene-1-carboxylic acid (III), m. p. 50·5°, previously determined under the same conditions.

Volatile oil (mg.)	5	10	15	20	30	40	50	75	100
(I) and (II) (mg.)	15·0	28·5	41·7	54·1	78·3	101·0	123·0	174·0	224·0
Yield, % of theory	69·5	73·1	75·0	77·1	79·8	82·5	84·7	89·8	93·0

The residual solution in the flask contained the hydrolysis products of the acyl esters of dihydroxystearic acid and was reserved for the estimation of the latter.

(b) *Spectrophotometric method.* On the assumption that the pure keto-acids have $E^{1\%}_{1\,cm.}$ 540 (ε 16,000) at 224 mμ, their percentage concentration is given by $(E^{1\%}_{1\,cm.} - B)/5{\cdot}4$, where B is the $E^{1\%}_{1\,cm.}$ value of the original elaidic acid at this wave-length. B was usually 1·25—1·5 (2·0 when admixed with 0·5% of Co). Since the absorption at 224 mμ by these products is due almost exclusively to the group •CH:CH•CO•, the percentage by weight of this group is given by $0{\cdot}03375(E^{1\%}_{1\,cm.} - B)$, or of •CO• thus conjugated by $0{\cdot}01751(E^{1\%}_{1\,cm.} - B)$.

All measurements were made with a Unicam SP. 500 Spectrophotometer, ethanol being the solvent.

9 : 10-*Dihydroxystearic Acid.*—(*a*) The solution remaining after the hydrolysis of the keto-acids (I) and (II) (above) was diluted to 100 ml. and brought to pH 8·0 with dilute sulphuric acid. The dihydroxystearic acid was then estimated by distillation with potassium periodate (King, *Nature*, *loc. cit.*), the amount of nonaldehyde recovered being corrected for that due to (i) the small amount of dihydroxy-acid resulting from the partial hydrolysis of elaidic acid oxide, and (ii) 9 : 10-ketol derivatives of stearic acid. The equilibrium mixture, m. p. 65°, of 10-hydroxy-9-oxo- and 9-hydroxy-10-oxo-stearic acids (into which either component is converted rapidly

by boiling alkali) was found by preliminary experiments to give 18% (wt.) of nonaldehyde on oxidation with periodate under the same conditions and this factor was used in computing the usually small correction.

(*b*) *Isolation method.* The solution remaining after the determination of the saponification value (for which *ca.* 1 g. was refluxed with ethanolic potassium hydroxide for 1 hr. in the usual way) was diluted, acidified, and cooled at 0° for at least 24 hr. The precipitate was washed successively with water, 50% ethanol and ether until free from oil, epoxide, etc., dried, and weighed. The nearly pure dihydroxystearic acid was dissolved in hot ethanol and the weight of the residue of silica, if any, subtracted from the total. A single crystallisation from ethanol generally sufficed to give a product, m. p. 129—130°, of nearly theoretical equivalent weight.

Ketol.—(*a*) The autoxidation product (*ca.* 2 g.), dissolved in cold 0·2N-sodium hydroxide (100 ml.) and brought to pH 8·0, was distilled with potassium periodate (0·2 g.) into the special trap until 20 ml. of distillate had been collected. The volume of oil in the trap was corrected for that due to pre-formed neutral volatile oil as found above, and the mass of nonaldehyde (*d* 0·827) arising from the oxidation of the ketol (King, *J.*, 1936, 1791) was calculated. The corresponding mass of the 9 : 10-ketol was then found by dividing by 0·18. The nonaldehyde gave a 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 104—106°.

(*b*) Oxygen was passed through elaidic acid at 78° for 6 days. The oily product contained 8·1% of ketol and reduced Fehling's solution fairly strongly. 2 : 4-Dinitrophenylhydrazine (7 g.) in sulphuric acid (52·5 ml.) was gradually added to the product (14 g.) in ethanol (280 ml.) with shaking and cooling. After 14 days the precipitate was washed with ethanol and crystallised from ethanol–chloroform, giving orange-red needles, m. p. 133—135°, raised to 137—142° on admixture with the dinitrophenylosazone of the 9 : 10-ketol derivative of stearic acid (m. p. 146·5°; King, *loc. cit.*) (Found: C, 54·0; H, 5·8; N, 16·5. Calc. for $C_{30}H_{40}O_{10}N_8$: C, 53·6; H, 6·0; N, 16·7%); it gave a characteristic violet colour with ethanolic sodium hydroxide.

Carbonyl [cf. Smith and Mitchell, *Analyt. Chem.*, 1950, **22**, 750; Schultes, *Z. angew. Chem.*, 1932, **47**, 258; O'Neill, "The Autoxidation of Drying Oils II" (Technical Paper No. 155, The Research Assocn. of British Paint, Colour, and Varnish Manufacturers), p. 418].—The product (*ca.* 0·25 g.) was accurately weighed in a stoppered flask. Ethanol (25 ml.) and 0·04% bromophenol-blue indicator (10 drops; 0·25 ml.) were added and the solution was brought to pH 3·7 (blue-green) with 0·1N-sodium hydroxide. A blank, omitting only the carbonyl compound, was prepared similarly. To each was added a 10% solution of hydroxylamine hydrochloride in 75% ethanol (10 ml.), and the solutions were titrated to pH 3·7 with 0·1N-sodium hydroxide after 5 and again after 30 min., the total volumes of alkali added being recorded. The percentage of CO in the substance was given by $0{\cdot}28(T - B)/m$, where T and B were the actual and blank titrations (ml.) respectively and m the mass of substance taken.

By conducting the reaction in the cold and limiting the time to 30 min., the effect of hydroperoxides was minimised. Under these conditions, one mole of *tert.*-butyl hydroperoxide liberated only 0·5 equiv. of acid from hydroxylamine hydrochloride, *i.e.*, 16 g. of active oxygen were equivalent to 14 g. of carbonyl. Thus, in view of the small peroxide content of the autoxidation products, it was deemed sufficiently accurate to correct the apparent CO values by subtracting seven-eighths of the active oxygen values.

The following results were obtained on synthetic keto-acids, only 0·1—0·2 g. of material being used:

		trans-11-Oxoheptadec-9-ene-1-carboxylic acid (III)	*trans*-11-Oxoheptadec-8-ene-1-carboxylic acid (λ-oxoelaidic acid), m. p. 73°	9 : 10-Ketol from stearic acid (m. p. 65°)
CO (%)	Found	9·42	9·23	8·57
	Calc.	9·46	9·46	8·91

Where the carbonyl content is small, all the above quantities may be doubled with the exception of the indicator, which should be kept constant.

Carbonyl due to "other" oxo-acids was calculated by subtracting from the total that due to η- and κ-keto-acids, ketol, and neutral volatile oil (nonanaldehyde and nonan-2-one).

Oxiran-oxygen.—The method of estimation was based on the absorption of hydrogen chloride in dioxan, with appropriate corrections for that absorbed by α-ethylenic ketones (King, *J.*, 1951, 1980).

Active Oxygen.—Lea's method ("Rancidity in Edible Fats," 1938, p. 107) was adapted for use with 0·1—0·2 g. of material.

Steam-volatile Acids.—The autoxidation product (1—2 g.) was distilled with water (150 ml.)

into 0·25N-sodium hydroxide (10 ml.) until most of the water (125 ml.) had distilled over. More water (125 ml.) was then added to the flask and distillation was continued until only 25 ml. remained in the flask. The excess of alkali in the distillate was then determined by titration. Although elaidic acid itself is very slightly volatile in steam, errors from this source were usually negligible.

Non-volatile, Water-soluble Acids.—The residue in the flask from the preceding operation was diluted with water (*ca.* 25 ml.) and set aside for 24 hr. After filtration, the insoluble matter was washed with cold water, and the combined filtrate and washings were titrated with 0·1N-sodium hydroxide.

Carbon Dioxide.—The barium carbonate was collected on a filter, washed, dried, and weighed, the filtrate and washings being reserved.

Formic Acid.—The filtrate and washings from the barium carbonate were neutralised with hydrochloric acid and diluted to 1 litre. The formate in this was estimated by the mercuric chloride method ("Official Methods of Analysis of the Association of Official Agricultural Chemists," Washington, 1950, p. 459).

Qualitatively, formate was recognised by the chromotropic acid, mercuric chloride, ferric chloride, silver nitrate and permanganate tests.

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The Anomalous Osmotic Behaviour of Polymethacrylonitrile.

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Reliable determinations of the number-average molecular weight of polymethacrylonitrile are not possible from osmotic-pressure measurements in ethyl methyl ketone solution. With this solvent, S-shaped π/c against c curves are obtained which cannot be satisfactorily extrapolated to zero concentration. The shape of these curves, the effect of temperature, and the peculiar solution properties of this system have been explained qualitatively in terms of competing polymer–solvent and polymer–polymer association.

*cyclo*Hexanone and acetone are the only two solvents in which polymethacrylonitrile exhibits normal osmotic and solution behaviour. Of these, the former has been found to be entirely satisfactory for the osmotic determination of molecular weights.

IN the general investigation of polymeric reactions, and particularly in kinetic work in this field, it is usually convenient to be able to measure number-average molecular weights which may be most readily deduced from osmotic pressure measurements. On plotting π/c against c (where π is the osmotic pressure of a solution of concentration c) non-ideal behaviour is invariably encountered, most polymer–solvent systems, however, being fairly well represented either by the linear expression $\pi/c = P + Qc$ or by $\pi/c = P + Qc + Rc^2$, which have been given ample theoretical justification by Huggins (*Ind. Eng. Chem.*, 1943, **35**, 216, 980). At all events, the linear or gently curved plots are usually fairly easily extrapolated to zero concentration, the intercept on the π/c axis, $(\pi/c)_0$ $(= P)$, being used to calculate the molecular weight of the solute from the classical equation $(\pi/c)_0 = \boldsymbol{R}T/M$.

The number of solvents for polymethacrylonitrile is restricted, the interaction between chains which causes the almost complete insolubility of polyacrylonitrile being only slightly eased by the introduction of the methyl group. Polymethacrylonitrile swells in chloroform, is soluble in cold solutions of methylene chloride and ethyl methyl ketone, and is freely soluble only in acetone and *cyclo*hexanone. Of these last four solvents methylene chloride and acetone present certain difficulties in osmotic work owing to their volatility. Ethyl methyl ketone and *cyclo*hexanone therefore appeared to be most suitable for routine measurements.

In ethyl methyl ketone at 23°, polymer A ($M = 63{,}000 \pm 2{,}000$, see p. 2125) is found to give the completely novel type of curve shown in Fig. 1 (curve 1). This curve can be

delineated accurately and reproducibly on a much wider vertical scale than that shown, so that there can be no doubt about the principal details of its shape. Also on Fig. 1 (curves 2 and 3) can be seen the marked changes which take place in the shape of the osmotic pressure curves with temperature. It is quite clear then that at the most convenient temperatures for osmotic pressure measurement (20—30°) an accurate extrapolation to zero concentration would be impossible, while even at 4° the fact that the slope is increasing with decreasing concentration at low concentrations would make the value of any extrapolation extremely doubtful.

Also in Fig. 1 are curves (4 and 5) obtained with solutions in *cyclo*hexanone, which exhibit normal behaviour, the slopes increasing with temperature but giving intercepts identical within experimental error. This intercept is obviously a reasonable one for the ethyl methyl ketone curves at 4° and 23°, and it must be assumed that at some lower concentration the 30° curve bends upwards also towards this ultimate value, which represents

FIG. 1. Osmotic curves for Polymer A ($M = 63{,}000 \pm 2{,}000$) in ethyl methyl ketone (1, 23°; 2, 4°; 3, 30°) and in *cyclo*hexanone (4, 30°; 5, 35°).

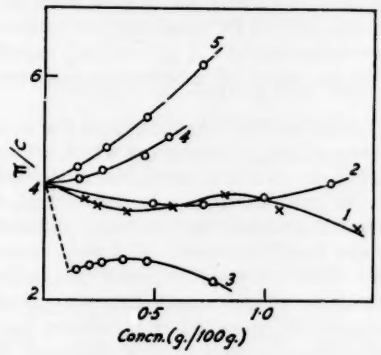
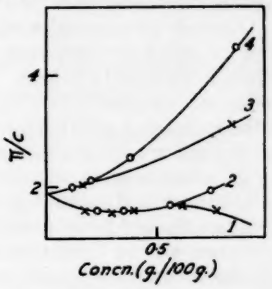


FIG. 2. Osmotic curves for Polymer B ($M = 137{,}000 \pm 5{,}000$) in ethyl methyl ketone (1, 24·5°; 2, 4°) and in *cyclo*hexanone (3, 25°; 4, 35°).



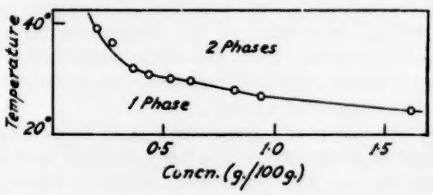


FIG. 3. Solubility of Polymer A in ethyl methyl ketone.

a molecular weight of 63,000 ± 2,000. Fig. 2 includes a similar series of curves derived from measurements made on polymer B ($M = 137{,}000 \pm 5{,}000$; see p. 2125).

An interesting property of the ethyl methyl ketone–polymethacrylonitrile system, and one which is clearly associated with its anomalous osmotic behaviour, is the fact that solubility increases with decreasing temperature. A 1% solution prepared at 4° becomes quite cloudy at 28° but remains crystal clear at −78°; it may be significant that ethyl methyl ketone is one of those substances which give a completely closed mutual solubility curve with water (Rothmund, *Z. physikal. Chem.*, 1898, **26**, 433).

The solution properties of polymers make it difficult to obtain accurate solubility curves by conventional methods. Precipitation in such systems takes place by the gradual aggregation of molecules over a fairly wide temperature range. Some arbitrary definition of precipitation must therefore be made for convenience, and the simplest in the present case is concerned with the visual appearance of cloudiness. Fig. 3 records a solubility curve obtained by slowly warming and cooling solutions of polymer A and plotting the average of the temperatures at which cloudiness appears and disappears in each case. These pairs of

temperatures were always within 1—2° of each other. When cloudiness appears the molecular aggregates must have become quite large and it is to be expected that the osmotic pressure of the system should be falling fairly rapidly with increasing concentration. There is at least qualitative agreement in this respect between the data in Fig. 3 and the ultimate decrease in π/c at high concentration shown by the ethyl methyl ketone curves in Fig. 1. Even at the lowest concentrations, however, the beginnings of precipitation are discernible from the decreasing values of π/c with increasing concentration, although the reason for the inflexions in the curves between these two extremes of concentration requires further consideration.

The amount of aggregation, or the number of aggregative interactions between molecules, obviously increases with concentration so that we may write $\alpha = f(c)$, where α is the number of aggregative interactions between different molecules per mole of polymer, and $f(c)$ is some function of concentration which increases with concentration. It follows that $\text{C.L.} = \text{C.L.}_0/(1 - \alpha) = \text{C.L.}_0/[1 - f(c)]$ where C.L. and C.L._0 are the average numbers of monomer units in molecular aggregates and single molecules respectively, *i.e.*, at concentrations c and zero. As the concentration increases from zero, the effect of this function is to give a negative slope to the curve of π/c against c. With increasing concentration, however, at low concentrations this negative slope increases only slightly and is soon overtaken by the rapidly increasing positive slope due to the terms Qc and Rc^2 resulting in a point of inflexion followed by a positive slope. As $f(c)$ approaches unity $\text{C.L.}_0/[1 - f(c)]$ rapidly approaches an infinitely high value, resulting in another point of inflexion and a rapid decrease in π/c, ultimately to zero.

The effect of temperature on the ethyl methyl ketone curves is explicable in the same terms as the increasing solubility with decreasing temperature. Substances which are not composed of giant or highly cross-linked molecules are freely soluble or insoluble respectively according as solute–solvent or solute–solute interaction predominates. In this system, in which both solvent and solute are relatively highly polar, polymer–polymer and polymer–solvent interactions are fairly strong and apparently also finely balanced. At lower temperatures polymer–solvent interaction predominates. Thus polymer–polymer interaction tends to be suppressed, agglomeration is largely prevented, and the osmotic curves approach normality. As the temperature is raised, polymer–solvent association is broken down progressively, allowing the less mobile polymer molecules to interact. Thus, although the effect of temperature increase will also be to make polymer–polymer interactions weaker, it also enables interaction between individual molecules at an increasing number of points by reason of the progressive removal of solvent from the environment of polymer molecules. In the range of temperatures studied, the latter process evidently prevails, giving the solubility and osmotic characteristics reported above.

While S-shaped osmotic curves of this type have not previously been reported, negatively sloping curves or parts of curves have been observed in a few instances and in each case have been explained by molecular association; *e.g.*, Steurer (*Z. physikal. Chem.*, 1942, **190**, 1) found that the osmotic pressure curves for ethyl cellulose in benzene and toluene are normal positively sloping straight lines down to concentrations of about 0·1—0·2%, below which they curve steeply upwards to very much higher values of π/c. The ultimate value at zero concentration is believed, although not proved, to be the same as that obtained when using solvents giving normal curves, so that, as in the present work, association appears to exist in the form of a dynamic equilibrium. By contrast with this, Doty (*J. Amer. Chem. Soc.*, 1947, **69**, 1631) has had to postulate a static association of polyvinyl chloride molecules in dioxan. In this case, the slope of the linear osmotic pressure curves decreases with temperature until at 14° a negative slope is obtained. Instead of giving a constant intercept on the π/c axis, however, $(\pi/c)_0$ decreases with decreasing temperature. Hence, even at the lowest concentrations association shows no signs of breaking down.

Experimental

Methacrylonitrile was prepared by acetylation of acetone cyanohydrin followed by pyrolysis of the resulting acetate. Acetone cyanohydrin (1 mol.) and acetic anhydride (1·5 mol.) were allowed to react at room temperature for 24 hr. Distillation of the resulting mixture gave an

acetone cyanohydrin acetate fraction (b. p. 180—185°). This was passed dropwise into a vertical silica tube about 4′ long and 3″ in diameter, which was packed with silica chips and heated electrically to 550°. The mixture collected at the bottom was poured into water, and the monomer extracted with ether, the ether extract being washed with water and dried (Na_2SO_4). The ether was removed by distillation, and the fraction of methacrylonitrile distilling between 92° and 94° collected (yield, 70% on acetone cyanohydrin).

Polymers A and B were obtained by polymerising the above monomer *in vacuo*, after degassing and twice distilling it *in vacuo*, at 80° and 70°, respectively, and in presence of 0·2% of benzoyl peroxide as catalyst. Polymerisation was continued to approx. 15% conversion. The polymer was isolated by dissolving this mixture in acetone, pouring the solution into methyl alcohol–water (75 : 25), and drying the resulting powder at 80° in air.

Osmotic pressure measurements were made on a Fuoss–Mead type instrument as modified by Masson and Melville (*J. Polymer Sci.*, 1949, **4**, 323), bacterial cellulose membranes being used.

We thank Imperial Chemical Industries Limited, Billingham, for supplies of acetone cyanohydrin and details of the preparation of methacrylonitrile from it, made available through Dr. Coates. We also thank the D.S.I.R. for the award of a Maintenance Allowance (E. V.), and the University of Glasgow for the award of an I.C.I. Research Fellowship (N. G.), during the tenures of which this work was carried out.

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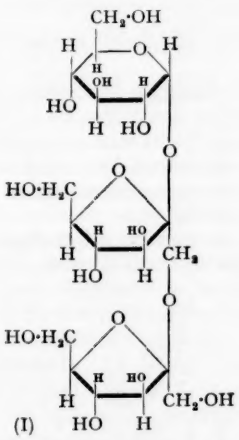
Studies of Aspergillus niger. *Part III.* The Structure of a Trisaccharide synthesised from Sucrose.*

By S. A. BARKER, E. J. BOURNE, and T. R. CARRINGTON.

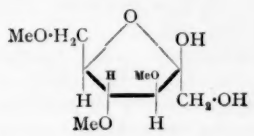
[Reprint Order No. 5111.]

One of the trisaccharides produced from sucrose by *Aspergillus niger* (152) has been characterised as *O*-α-D-glucopyranosyl-(1 ⟶ 2)-*O*-β-D-fructofuranosyl-(1 ⟶ 2) β-D-fructofuranoside.

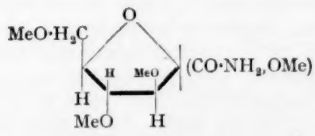
DURING a preliminary investigation of the carbohydrate metabolism of *Aspergillus niger* (strain 152), which synthesises nigeran, a polyglucosan in which most, if not all, of the α-1 : 4- and α-1 : 3-linkages are arranged alternately (Barker, Bourne, and Stacey, *Chem. and Ind.*, 1952, 756; Part I, *J.*, 1953, 3084), two trisaccharides (termed I and II) were



(I)



(II)



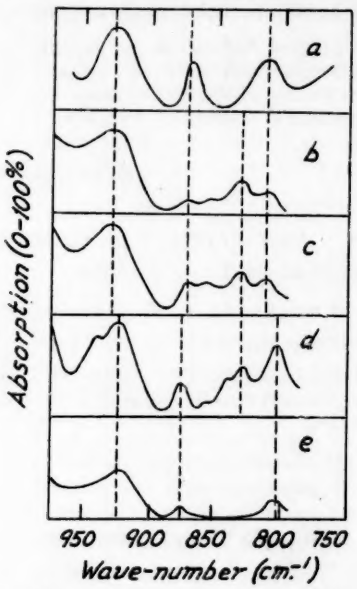
(III)

synthesised from sucrose by a cell-free extract of the mould (Barker and Carrington, Part II *). These trisaccharides, which were both non-reducing and contained two fructose residues and one of glucose, together with a tetrasaccharide fraction, containing

* Part II, *J.*, 1953, 3588.

three fructose residues and one of glucose, were considered to arise by a trans-fructosidase mechanism. The major component, trisaccharide I, has now been shown to be *O*-α-D-glucopyranosyl-(1 ⟶ 2)-*O*-β-D-fructofuranosyl-(1 ⟶ 2) β-D-fructofuranoside (I).

The crystalline trisaccharide I was methylated, first with methyl sulphate–sodium hydroxide, and subsequently with methyl iodide–silver oxide, as described for the methylation of kestose [*O*-α-D-glucopyranosyl-(1 ⟶ 2)-*O*-β-D-fructofuranosyl-(6 ⟶ 2) β-D-fructofuranoside] by Albon, Bell, Blanchard, Gross, and Rundell (*J.*, 1953, 24). The resulting undeca-*O*-methyltrisaccharide, hydrolysed with 0·05N-sulphuric acid, gave sugars having R_F values and colour reactions with spraying reagents identical with those of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose, and 3 : 4 : 6-tri-*O*-methyl-D-fructose. Chromatography on a silica column (Bell and Palmer, *J.*, 1949,



a, *Inulin*.
b, *Trisaccharide I*.
c, *Trisaccharide* α_1.
d, *Kestose*.
e, *Levan*.

2522) was employed to separate the tri-*O*-methylfructose (0·95 mol.) from the two tetra-*O*-methyl sugars (1·85 mol.).

The tri-*O*-methyl sugar was characterised as 3 : 4 : 6-tri-*O*-methyl-D-fructofuranose (II) by its physical constants, by its ability to form an *iso*propylidene derivative, by its phenylosazone, and by oxidation with periodate. The sugar consumed 0·91 mol. of the oxidant, and gave formaldehyde (0·91 mol.), isolated as its crystalline dimedone derivative (cf. Bell, *J.*, 1948, 992), together with 2 : 3 : 5-tri-*O*-methyl-D-arabonolactone, characterised as the amide (cf. Hirst, Mitchell, Percival, and Percival, *J.*, 1953, 3170).

Determination of the aldose component of the mixture of tetra-*O*-methyl sugars with alkaline hypoiodite (cf. Hirst, McGilvray, and Percival, *J.*, 1950, 1297) showed the aldose and ketose sugars to be present in equimolecular proportions, a conclusion which was confirmed by the optical rotation of the mixture. Further fractionation was effected by mild treatment with methanolic hydrogen chloride and fractional distillation, to give tetra-*O*-methylglucose and methyl tetra-*O*-methylfructofuranoside (cf. Haworth and Mitchell, *J.*, 1923, 301). Crystallisation of the former gave 2 : 3 : 4 : 6-tetra-*O*-methyl-α-D-glucose, which was characterised also as its aniline derivative. The fructoside was hydrolysed to the free sugar, which was shown to be 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructofuranose by conversion into crystalline methyl 3 : 4 : 6-tri-*O*-methyl-D-fructofuronamide (III) (cf. Avery, Haworth, and Hirst, *J.*, 1927, 2308).

Partial hydrolysis of trisaccharide I gave fructose, glucose, and a non-reducing disaccharide, which, after purification on a charcoal column, could not be distinguished

from sucrose by ionophoresis or chromatography; it had $[\alpha]_D$ +69°, compared with +66·5° quoted for sucrose. Hydrolysis of the disaccharide caused inversion of the rotation, and gave fructose and glucose in approximately equimolecular proportions.

On the basis of the above observations, the trisaccharide was assigned the structure (I). The only dubiety which exists concerns the anomeric character of the linkage between the fructose units; however, it is most probable that this link is β in view of the prevalence of β-fructofuranoside residues in Nature. Such a structure is consistent with the view that the trisaccharide was formed by the transfer of a fructofuranose residue from one molecule of sucrose to another.

The synthesis of oligosaccharides from sucrose by extracts of moulds has been reported by several workers (cf., for example, Bealing and Bacon, *Biochem. J.*, 1951, **49**, lxxv; 1953, **53**, 277; Wallenfels and Bernt, *Angew. Chem.*, 1952, **64**, 28; Pazur, *J. Biol. Chem.*, 1952, **199**, 217), but only one product has yet been rigorously characterised (by Bacon and Bell, *J.*, 1953, 2528); this was a trisaccharide ("α_1") produced from sucrose by "Takadiastase" (a commercial mould enzyme preparation), and it was proved to have a structure identical with that now assigned to our own trisaccharide I. Further evidence that I and α_1 are the same trisaccharide is provided by their optical rotations (I, +29·2°; α_1, +30·5°, +32·6°), by those of their methyl ethers (I, +27·3°; α_1, +27·9°), by chromatography, and by their infra-red spectra (see Figure), determined over the frequency range 780—980 cm.$^{-1}$ by the Nujol "mull" technique (cf. Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171); the sample of α_1 was kindly provided by Dr. Bacon. It will be seen that these spectra show a closer correspondence with that of inulin, as regards both the positions and the relative intensities of the peaks, than with those of levan and kestose (kindly supplied by Dr. Gross), both of which have a β-2 : 6-fructosidic linkage. All three trisaccharide samples, and also sucrose, show an absorption peak at *ca.* 840 cm.$^{-1}$, whereas the two polysaccharides do not; this is a peak (type 2*a*) given by α-anomers in the glucopyranose series (cf. Barker *et al.*, *loc. cit.*, 1954).

Experimental

Isolation of the Trisaccharide.—Details for the preparation of the enzyme extract, its incubation with sucrose, and the detection and fractionation of the synthetic oligosaccharides were reported in Part II (*loc. cit.*). Trisaccharide I was crystallised from methanol–ethanol; it showed $[\alpha]_D^{16}$ +29·2° (*c*, 0·58 in H_2O), and was non-reducing to the Shaffer–Hartmann solution (*J. Biol. Chem.*, 1921, **45**, 377). Hydrolysis with 0·005N-sulphuric acid at 80° for 6 hr. (to $[\alpha]_D^{16}$ −36·2°) yielded a ketose and an aldose, in the molar ratio 2·1 : 1 (Van der Plank, *Biochem. J.*, 1936, **30**, 460), having R_F values identical with those of fructose and glucose, respectively, when irrigated on a paper chromatogram with the upper phase of *n*-butanol (40%)–ethanol (10%)–water (49%)–ammonia (1%). The ketose and aldose sugars were detected with naphtharesorcinol (Partridge, *ibid.*, 1948, **42**, 238) and aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443), respectively.

Methylation of the Trisaccharide.—In a typical experiment, the crystalline sugar (1·27 g.) was methylated in dioxan (20 ml.) at 30° with 30% sodium hydroxide solution (120 ml.) and methyl sulphate (60 ml.), as described for kestose (Albon *et al.*, *loc. cit.*). The product (0·945 g.) was thrice methylated under reflux with methyl iodide (4 ml.) and silver oxide (5·3 g.), and isolated from the silver residues by ether-extraction. The extract was filtered and evaporated at 30° *in vacuo* to a syrup (0·802 g., 48%), $[\alpha]_D^{20}$ +27·3° (*c*, 0·95 in $CHCl_3$), n_D^{25} 1·4590 (Found: C, 53·3; H, 8·3; OMe, 51·3. Calc. for $C_{29}H_{54}O_{16}$: C, 52·9; H, 8·3; OMe, 51·8%). Infra-red analysis showed negligible absorption in the region of the OH stretching frequency (3400—3700 cm.$^{-1}$), a critical test for free hydroxyl groups.

Hydrolysis of the Methylated Trisaccharide.—A solution of the methylated sugar (0·778 g.) in 0·05N-sulphuric acid (25 ml.) was heated at 95—100° for 75 min. (to $[\alpha]_D^{20}$ +43·9°, constant). After neutralisation with barium carbonate, paper-chromatographic analysis of the filtrate, as above, revealed a single aldose and two ketose components, identical in R_F values and spray reactions with reference spots of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (R_F 0·86), 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose (R_F 0·88), and 3 : 4 : 6-tri-*O*-methyl-D-fructose (R_F 0·77). On the basis of the respective reported values for $[\alpha]_D$ [+81·3° (West and Holden, *Org. Synth.*, 1940, **20**, 97); +30·3° and +29·5° (Bell, *J.*, 1953, 1231)], the observed equilibrium value for an equimolar mixture of these sugars should have been +50·0°.

Chromatography on a column of silica gel (Bell and Palmer, *loc. cit.*) was employed to separate the tri-*O*-methylfructose from the tetra-*O*-methyl components. The silica gel (25 g.), prepared by Tristram's method (*Biochem. J.*, 1946, **40**, 723), was ground to a powder with water (15 ml.), suspended in toluene (100 ml.) containing 0·33% of ethanol, and closely packed into a column (12 × 3 cm.). The syrupy hydrolysate (0·773 g.) in toluene–ethanol (10 ml.) was allowed to diffuse into the column, which was developed with more toluene–ethanol (4 l.). The eluate was concentrated *in vacuo* at 30° over barium carbonate, filtered, and evaporated to a syrup (0·514 g.). Chromatographic analysis showed the presence of components corresponding to tetra-*O*-methyl-D-glucose and tetra-*O*-methyl-D-fructose, but none of the tri-*O*-methyl component. An aliquot of the syrup (9·53 mg.), treated with alkaline hypoiodite by a method essentially that of Hirst, McGilvray, and Percival (*loc. cit.*), was shown to contain 4·81 and 4·72 mg. (by difference) of the glucose and the fructose derivative, respectively. The mixture had $[\alpha]_D^{21}$ +54·5° (*c*, 0·95 in H_2O), compared with the theoretical value +55·8° for an equimolar mixture of tetra-*O*-methyl-D-glucose and tetra-*O*-methyl-D-fructose. The tri-*O*-methyl component was recovered from the column by elution with methanol (1·5 l.), and the eluate concentrated to a syrup (0·250 g.), shown to be chromatographically pure.

The mixture of tetra-*O*-methyl sugars was fractionated further by Haworth and Mitchell's method (*loc. cit.*). Accordingly, the syrup (0·386 g.) in dry methanolic hydrogen chloride (0·25% w/w; 20 ml.) was kept at room temperature until constant optical rotation (68·9°) was attained (5 days). The expected equilibrium rotation for the mixture, based on the $[\alpha]_D$ values of +81·3° (West and Holden, *loc. cit.*) and 57·7° (Haworth and Mitchell, *loc. cit.*), is +71·2°. The solution was neutralised with silver carbonate, filtered, and evaporated at 30° *in vacuo* to a syrup, which was fractionally distilled at 0·2 mm. The methyl tetra-*O*-methyl-D-fructofuranoside fraction (0·175 g.; b. p. 64—70°), collected in a receiver cooled in liquid air, was shown to be chromatographically pure (R_F 0·93); the residual tetra-*O*-methyl-D-glucose was contaminated with a little of the fructoside. A repetition of this experiment gave similar results.

*Characterisation of the Tri-*O*-methylfructose.*—(*a*) The syrup showed $[\alpha]_D^{20}$ +26·0° ⟶ +29·3°, 24 hr. (*c*, 0·62 in H_2O) (Found: OMe, 42·4. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Hirst, Mitchell, Percival, and Percival (*loc. cit.*) recorded $[\alpha]_D$ +27·0° ⟶ +29·0° (in H_2O) for 3 : 4 : 6-tri-*O*-methyl-D-fructose.

A portion (0·0377 g.) in anhydrous acetone (5 ml.) containing 0·5% of hydrogen chloride (w/w) showed $[\alpha]_D^{19}$ +31·8° ⟶ +63·7° (240 min.), indicating the formation of an *iso*propylidene derivative. Montgomery (*J. Amer. Chem. Soc.*, 1934, **56**, 419) gave $[\alpha]_D$ +70° for 3 : 4 : 6-tri-*O*-methyl-1 : 2-*O*-*iso*propylidene-D-fructofuranose.

(*b*) Oxidation of the tri-*O*-methylfructose (0·0245 g.) in 0·075M-phosphate buffer (10 ml.; pH 7·42) with 0·1M-sodium metaperiodate (5 ml.), by Bell's method (*J.*, 1948, 992), gave formaldehyde, isolated as the dimedone derivative (0·91 mol.), m. p. and mixed m. p. 189—191°. A further specimen (0·2544 g.), treated with 0·5M-sodium metaperiodate (15 ml.) in the dark at room temperature, by the method of Hirst *et al.* (*J.*, 1953, 3170), consumed 0·91 mol. of periodate (72 hr.), and gave 2 : 3 : 5-tri-*O*-methyl-D-arabonolactone (0·117 g.), which was characterised as the amide, m. p. 137—138°, not depressed in admixture with an authentic specimen (kindly provided by Mrs. E. E. Percival) (Found: C, 46·3; H, 8·1; N, 6·3. Calc. for $C_8H_{17}O_5N$: C, 46·4; H, 8·3; N, 6·8%).

(*c*) The sugar (0·076 g.) in water (3 ml.) and acetic acid (0·5 ml.) was heated at 70° for 2·5 hr. with phenylhydrazine (0·15 ml.), to give an osazone (0·046 g.), which after recrystallisation from anhydrous ether–light petroleum (b. p. 40—60°) had m. p. 130—132°, not depressed in admixture with an authentic specimen of 3 : 4 : 6-tri-*O*-methyl-D-fructose phenylosazone prepared by the late E. G. V. Percival.

*Characterisation of the Tetra-*O*-methylfructose.*—The methyl tetra-*O*-methyl-D-fructofuranoside (0·230 g.) was hydrolysed at 100° with 0·05N-H_2SO_4 (10 ml.), $[\alpha]_D^{18}$ +55·8° ⟶ +27·3° (0·5 hr.) (*c*, 4·60 in H_2O). Bell (*loc. cit.*) reported $[\alpha]_D$ +30·6° (equil., in H_2O) for 1 : 3 : 4 : 6-tetra-*O*-methyl-D-fructose. The solution was neutralised with barium carbonate, filtered, and evaporated under diminished pressure, to give the tetramethyl ether as a syrup. A larger quantity was prepared in a second experiment. Oxidation of a sample (0·755 g.) with nitric acid (*d* 1·42; 8 ml.), followed by esterification, methylation, and fractional distillation (0·1 mm.), using the procedure of Avery, Haworth, and Hirst (*loc. cit.*), yielded two fractions (b. p. 75—82°, 0·282 g.; b. p. 82—90°, 0·302 g.). These were dissolved separately in methanol (3 ml.), saturated with ammonia (0°), and refrigerated (3 days). Evaporation of the solvent, and recrystallisation of the product from ethanol–ether, yielded, mainly from the second fraction,

methyl 3 : 4 : 6-tri-*O*-methyl-D-fructofuronamide (0·118 g.), m. p. 100—101°, alone and in admixture with an authentic specimen supplied by Mrs. E. E. Percival (Found : C, 48·2; H, 7·4; N, 5·7. Calc. for $C_{10}H_{19}O_6N$: C, 48·2; H, 7·7; N, 5·6%).

Characterisation of the Tetra-O-methylglucose.—(*a*) The tetra-*O*-methyl-D-glucose (0·431 g.), purified by distillation, was recrystallised from ether–light petroleum, and gave 2 : 3 : 4 : 6-tetra-*O*-methyl-α-D-glucose (0·195 g.), m. p. and mixed m. p. 86—89°, $[\alpha]_D^{19}$ +89·1° ⟶ +82·5° (24 hr.) (*c*, 0·61 in H_2O) (Found : C, 50·9; H, 8·6. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5%).

(*b*) The crystalline tetramethyl ether (0·110 g.), treated with aniline (Peat, Schlüchterer, and Stacey, *J.*, 1939, 581), gave 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-glucosylamine (0·019 g.), m. p. and mixed m. p. 133—135°.

Partial Hydrolysis of Trisaccharide I.—The trisaccharide (0·606 g.) was heated at 80° for 1 hr. with 0·005N-sulphuric acid (25 ml.). Only one disaccharide, having an R_F value and spray reactions identical with those of sucrose, was observed on a chromatogram of the neutral hydrolysate. This disaccharide was separated from the glucose and fructose also present by gradient elution (Alm, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826) on a charcoal column, using 0—5% aqueous ethanol. Two fractions were obtained, one (0·425 g.) consisting of the monosaccharides, and the other (0·130 g.) containing the ionophoretically- and chromatographically-pure disaccharide. The disaccharide, hydrolysed with 0·05N-sulphuric acid at 90°, showed $[\alpha]_D$ +69·0° ⟶ −26·8° (2 hr.) (*c*, 0·52 based on reducing sugars in the hydrolysate). Analysis of the hydrolysate (see above) showed the molar ratio of ketose to aldose to be 1·18 : 1; these two sugars were chromatographically identical with fructose and glucose, respectively.

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Solubilization of Water in Non-polar Solvents by Detergent Mixtures.

By SANTI R. PALIT and V. VENKATESWARLU.

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It was expected, on the basis of Winsor's theory, that a combination in suitable proportions of a hydrophilic and a lipophilic detergent would show considerably increased solubilizing power. This is experimentally confirmed by studying the solubilization of water in non-polar solvents by means of binary mixtures of dodecylammonium chloride, formate, acetate, laurate, or oleate; the detergent mixtures considerably increase the solubility although the separate constituents alone have but little effect. This effect is observed only for mixtures of a hydrophilic (*e.g.*, dodecylammonium chloride, formate, and acetate) and a lipophilic (*e.g.*, the laurate and oleate) detergent, but not where both the "amphiphiles" are either hydrophilic or lipophilic. These results constitute strong support to Winsor's theory of solubilization and demonstrate the utility of the conception of the ratio, *R*, introduced by him, in understanding the various phenomena.

Freezing-point data obtained with mixtures of detergents show that there is little change on mixing in the average degree of association of the two individual detergents. Thus increased solubility does not necessarily mean the existence of more micelles, and it is suggested that micelle formation and solubilization are parallel phenomena originating from the same cause, *viz.*, the inherent tendency of soap molecules to associate either with themselves or with other molecules.

WINSOR (*Trans. Faraday Soc.*, 1948, **44**, 376, 382, 387, 390) and Palit (*J. Colloid Sci.*, 1949, **4**, 523) observed that solubilization by amphiphiles is greatly increased in mixed solvents even though the amphiphiles have little solubilizing power in the individual solvents. An

explanation of this phenomenon has been advanced by Winsor in terms of his general theory of solubilization on the basis of the lipophilic–hydrophilic affinity ratio R, where $R = A_{C\bar{O}}/A_{C\bar{W}}$, in which C represents the detergent, $\bar{O}$ the oily phase, and $\bar{W}$ water, and the A terms represent the affinities denoted by their subscripts. Winsor further resolves each of these affinities into two parts, one due to hydrophilic attraction, A_H, originating from hydrogen bonding, and another due to lipophilic attraction, A_L, originating from van der Waals forces, and his final formulation for R is

$$R = A_{C\bar{O}}/A_{C\bar{W}} = (A_{L,C\bar{O}} + A_{H,C\bar{O}})/(A_{L,C\bar{W}} + A_{H,CW}) \quad . \quad . \quad . \quad . \quad (1)$$

According to Winsor, maximum solubilization occurs where R is near unity, and any system with $R < 1$ gives a predominantly hydrophilic system (called Type I system by Winsor) whereas with $R > 1$ the system becomes predominantly lipophilic (Type II system). It is evident that, for a mixture of two solvents to show enhanced solubilization, one should form a Type I system ($R < 1$) and the other a Type II system ($R > 1$), and this is found to be the case.

If Winsor's theory is correct, similar considerations must hold as regards solubilization by mixtures of detergents. Our earlier work (*Proc. Roy. Soc.*, 1951, **208**, *A*, 542) on solubilization by dodecylamine soaps of fatty acids (C_1 to C_{18}) has shown the significance of the ratio R in governing the extent of solubilization. It has been found that dodecylammonium butyrate exhibits maximum solubilizing power when R is presumably closest to unity, and the dodecylamine salts of lower and higher fatty acids solubilize but little and form systems of respectively Type I and Type II.

Evidently, the condition that R should approximate to unity can also be achieved by suitably mixing the two extreme types of detergent, and it might be expected that a poorly solubilizing Type I-forming detergent and a poorly solubilizing Type II-forming system would show greatly enhanced solubilization when mixed in appropriate proportions. Winsor (*loc. cit.*) himself observed this feature qualitatively with mixtures of aerosol OT and sodium undecanoate. The present paper reports the results of a systematic study of solubilization by mixtures of detergents where the individual detergents are known to form either Type I or Type II systems. These observations also open up the possibility of putting the micellar theory of solubilization to a critical test by simple physicochemical measurements, and the results of such a test are also reported.

Experimental

The detergents used were dodecylammonium formate, acetate, laurate, oleate, and chloride, prepared in the usual manner by mixing equivalent quantities of the amine and acid in light petroleum. The solvent was evaporated off and the detergents were dried in a vacuum. In preparing the hydrochloride, the amine and acid were allowed to react in a small quantity of freshly distilled absolute alcohol and, when the reaction was complete, the detergent was precipitated by acetone, washed with small amounts of light petroleum, and dried in a vacuum. All the detergents are white crystalline compounds at room temperature except the oleate which is an orange-brown liquid. Dodecylamine (supplied by Armour & Co., of U.S.A.) and the fatty acids (White Label, Eastman Kodak Co.) were used after purification by conventional methods.

Solubilization measurements were carried out in the usual manner (Palit and Venkateswarlu, *loc. cit.*; Palit and McBain, *J. Soc. Chem. Ind.*, 1947, **66**, 3), 5 c.c. of the solution containing 0·5 g. of the detergent (sometimes 10 c.c. containing 1 g.) being used, and solubilizing power is expressed as the weight of water solubilized per g. of detergent (pure or mixture). After the limit of solubilization has been attained, the type formed, *i.e.*, whether I or II, is determined in each case. In Winsor's terminology, these types respectively indicate whether the system is predominantly aqueous or non-aqueous. This was ascertained by adding a drop of oleic acid to the turbid detergent solution saturated with water and observing whether the system clears or further clouds, this indicating Type I and II, respectively. This test is also supplemented by electrical conductivity and miscibility (in water and organic solvent) tests. The types formed are indicated in the curves (Figs. 1—4) by the corresponding Roman numeral near each experimental point.

Results and Discussion

Mixtures of Detergents of Opposite Types.—Figs. 1—4 represent the data of solubilization of water in solvents such as toluene and carbon tetrachloride by detergent mixtures. All the measurements were at 40° unless otherwise stated. For economy of space actual data are omitted but the values are ascertainable from the graphs.

Fig. 1. *Solubilization of water in toluene at 40° by dodecylammonium formate–laurate (A) and acetate–laurate (B) mixtures.*

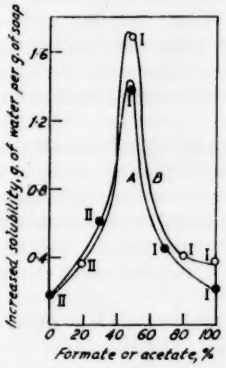

Fig. 2. *Solubilization of water at 40° by dodecylamine soaps; A, formate–oleate in toluene; B, acetate–oleate in toluene; C, acetate–laurate in carbon tetrachloride.*

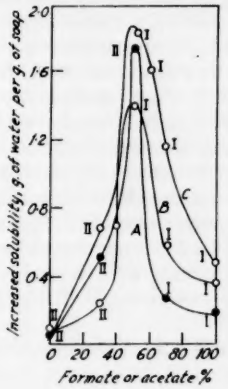

Fig. 3. *Solubilization of water at 35° by dodecylammonium chloride–oleate mixture in chloroform.*

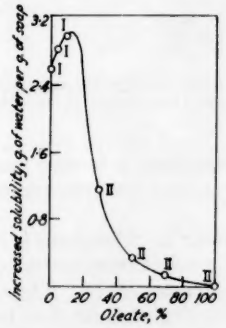

Fig. 4. *Solubilization of water at 40° by dodecylamine soaps: A, formate–acetate; B, chloride–acetate, in chloroform (ordinates for B, right-hand scale); C, formate–acetate in toluene. (All systems are of Type I.)*

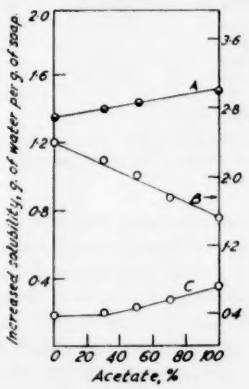

Fig. 1 shows the results obtained by using formate–laurate and acetate–laurate mixtures in toluene, and Fig. 2 those for formate–oleate and acetate–oleate mixtures in toluene and for acetate–laurate mixtures in carbon tetrachloride. Figs. 1 and 2 show that the foregoing four detergents have only a slight effect individually but show pronounced solubilization when suitably admixed. For instance, the acetate and laurate separately solubilize 0·364 and 0·179 g. of water respectively per g. of soap, but a 1 : 1 (wt.) mixture solubilizes 1·68 g., which is about 6 times greater than the mean of these values. Similar behaviour is found for the other three combinations mentioned above. From the graphs it is seen that all these curves show peak solubilization when the constituent detergents are present in

approximately equal weight, the peak solubilities for such formate–laurate, acetate–oleate, and formate–oleate mixtures being respectively 1·38, 1·392, and 1·728 g. of water per g. of soap, *i.e.*, about 7, 4, and 7 times the amounts to be expected from the means.

It is also seen from the graphs that acetate and formate invariably form Type I systems ($R < 1$), and laurate and oleate Type II ($R > 1$) systems. Admixture of these two classes of detergents would produce, at some suitable proportion, a system having the ratio, R, close to unity, and hence, according to Winsor's theory, would give rise to a maximum in the solubilization curve for the mixture. The fact that the solubilization-increase curve is more or less symmetrical indicates that the detergents formate and acetate are roughly as strongly hydrophilic as laurate and oleate are lipophilic. These results are just what would be expected qualitatively from Winsor's theory and constitute strong evidence in its favour and show the utility of his concept of the ratio R.

It may be pointed out that the mixed detergent effect is not only analogous to that of mixed solvent effect observed by Palit (*loc. cit.*), but is fundamentally the same. In the former R is brought towards unity by suitably mixing the detergents, and in the latter the same result is accomplished by mixing solvents.

Effect of Solvent.—This mixed detergent phenomenon, though demonstrated above in only toluene and carbon tetrachloride, should also happen in other solvents, in fact, in any solvent wherever one of the detergents forms a Type I system and the other a Type II system. This has been shown to be the case with a large number of solvents by studying only three systems, *viz.*, the individual detergents and a 1 : 1 mixture by weight of the two. The results are given in Table 1, and, except in chloroform (see next paragraph), the

TABLE 1. *Solubilization of water by detergents and their* 1 : 1 *mixtures.**

Solvents	G. of H_2O solubilized per g. of detergent					
	Acetate	Laurate	1 : 1 Mixture	Formate	Oleate	1 : 1 Mixture
n-Hexane	0·149 (I)	0·239 (II)	1·62 (*a*)	0·062 (I)	<0·1 in all cases	2·576 (II)
n-Heptane	0·222 (I)	0·249 (II)	0·90 (I)	—		—
*cyclo*Hexane	0·904 (I)	0·270 (II)	1·37 (I)	0·125 (I)		1·65 (II)
Methyl*cyclo*hexane ...	0·906 (I)	0·176 (II)	0·90 (I)	—	All Type II systems	—
Benzene	—	—	—	0·228 (I)		1·7 (II)
Toluene	0·364 (I)	0·179 (II)	1·68 (I)	0·196 (I)		1·728 (II)
Xylene	0·320 (I)	0·189 (II)	1·43 (I)	—		1·808 (II)
Ethylbenzene	—	—	—	0·143 (I)		1·844 (II)
Chlorobenzene	—	—	—	0·23 (I)		1·78 (II)
Carbon tetrachloride	0·48 (I)	0·093 (II)	1·82 (I)	0·525 (I)		1·596 (II)
Chloroform	1·50 (I)	0·233 (II)	0·18 (II)	1·35 (I)		1·356 (II)
Tetrachloroethylene	—	—	—	—		1·5 (II)

* The type of system is indicated by Roman numerals; *a* denotes that the behaviour is ambiguous, the system responding to some tests of Type I and others of Type II systems—presumably R is very near to unity.

increase in solubilizing power is evident in all cases. Sometimes it is very marked; *e.g.*, in *n*-hexane the formate–oleate mixture gives a solubility at least 30 times greater than the mean value for the individual detergents.

Unsymmetrical Increase of Solubilization.—The behaviour in chloroform is exceptional in that the individual detergent, say the acetate, is a better solubilizer than a 1 : 1 mixture of acetate and laurate, the values being 1·5 g. and 0·18 g., respectively. The explanation is simple. Dodecylammonium acetate has higher affinity for chloroform than for the other solvents, as also shown by the high solubility of the long-chain amine salts in chloroform. In other words $A_{C\bar{O}}$ (eqn. 1) is higher, and so R has a higher value which makes it approach unity more closely though remaining at a value less than unity. Hence, a small addition of laurate ($R \gg 1$) produces peak solubilization and any further addition of laurate brings down the solubilization sharply. This results in a highly unsymmetrical solubilization curve. A 1 : 1 mixture lies on the falling branch of the solubilization curve and so it is not necessarily more powerful than any of the other detergent mixtures but may have all intermediate values.

Experimental support to the views expressed above is obtained by a study of a similar system, *viz.*, dodecylammonium chloride and oleate in chloroform (at 35°), the results of

which are shown in Fig. 3. Here the chloride forms a Type I system of appreciable solubilizing power, *i.e.*, R is very near to but less than unity. On the other hand, oleate forms a Type II system with very little solubilization, *i.e.*, R is greater than and far removed from unity. It may be expected on the basis of Winsor's theory and the above reasonings that only a small amount of oleate is required to increase to a maximum the solvent power of the system, and further quantities would only reverse the type and decrease solubilization; for instance, it is seen from Fig. 3 that a peak solubilization of 2·94 g. of water per g. of soap is attained at a proportion of 90 : 10 of the chloride and oleate respectively.

Mixtures of Detergents of the Same Type.—The detergent mixtures studied so far are those where one of the components forms a Type I system and the other a Type II system. If detergents which form the same type of system are combined, then only intermediate quantities are expected to be solubilized and no pronounced maximum should occur. Accordingly, detergent mixtures of dodecylammonium chloride, formate, and acetate were studied which are invariably found to form Type I systems. Results are shown in Fig. 4. It is seen that the amount of water solubilized varies almost linearly with the proportions of the individual detergents and increases as the proportion of the more solubilizing detergent increases. This constitutes another confirmation of Winsor's theory.

A Critical Test of the Micellar Concept of Solubilization.—The foregoing work suggests a critical experimental test of the micellar theory. It is generally conceded that micelle formation is the cause of solubilization. If that is so, we should expect that this profound increase in solubilization on mixing detergents would reveal highly increased micelle formation if examined by any of the cryoscopic methods. We have attempted to verify the foregoing deduction by freezing-point measurements and the results are described below. The electrical conductivity of quaternary salts in weakly polar organic solvents is extremely small (Strong and Kraus, *J. Amer. Chem. Soc.*, 1950, **72**, 166; Winsor, *Trans. Faraday Soc.*, 1950, **46**, 762) and so the results are free from any complication due to dissociation. The effect of the very small solubility of water in the solvents on freezing point was found to be small (0·03° for benzene and less than 0·01° for the other solvents) and was neglected.

TABLE 2. *Freezing-point depression and solubilization by detergent mixtures.*

Detergent : dodecylammonium salt	Solvent	G. of H_2O solubilized per 15 c.c. of soln.	F.p. depression, ΔT	α *	Solubilizing power
Propionate (A)	Benzene (5% soln.)	nil	0·205°	5·57	0·92 (10% soln.)
Oleate (B)	,,	,,	0·21	3·02	≃0
70% of (A) and 30% of (B)	,,	,,	0·23	4·81	1·76
	,,	,,	0·27	4·29	1·54
50% of (A) and 50% of (B)	,,	0·11	0·22	5·27	—
	,,	0·22	0·215	5·39	—
	,,	0·33	0·21	5·52	—
	,,	1·01	0·195	5·94	—
A	*cyclo*Hexane (1% soln.)	nil	0·10	10·1	1·5 (1% soln.)
B	,,	,,	0·11	5·1	nil
70% of (A) and 30% of (B)	,,	,,	0·10	8·6	2·0
	,,	0·10	0·10	8·6	—
Acetate (C)	Bromoform (1% soln.)	nil	0·04	5·1	1·0 (1% soln.)
Oleate (B)	,,	,,	0·06	1·8	nil
80% of (C) and 20 % of (B)	,,	,,	0·048	4·4	1·6
	,,	0·05	0·05	4·3	—

* α = Degree of association.

Freezing-point measurements were carried out first in benzene with dodecylammonium propionate and oleate and 7 : 3 and 1 : 1 (wt.) mixtures of the two, the former mixture being known to give a solubilization about twice the mean value. The results are presented in Table 2. Acetate or formate could not be used in this investigation owing to solubility limitations. It will be seen from the Table that the pure soaps are not highly associated, the average degree of association being about 4·2, a value close to previous

observations in similar systems (Palit and McBain, *loc. cit.*; Gonick, *J. Colloid Sci.*, **1946**, **1**, 393; Gilmour, Nelson, and Pink, *Nature*, **1953**, **171**, 1075). The most unexpected thing, however, is that the mixture gives a freezing-point depression which is practically the mean of the values for the two soaps. This definitely discounts the idea that a higher solubilizing power is necessarily associated with more micelle formation.

We next investigated by the same technique what happens when these systems solubilize water, and the results are also included in Table 2. It is seen that the first small portion of solubilized water increases the average degree of association, whereafter later additions of water cause no further change : the average degree of association of the mixture in a 5% solution is 4·3, and 0·11 c.c. of water solubilized in 15 c.c. of this solution increases the degree of association to 5·3 but this is not appreciably altered by further solubilization up to near saturation point, *i.e.*, 1·01 c.c. of water. Hence, we conclude that (*a*) solubilization does not run parallel with pre-existing micelles and (*b*) more solubilization does not necessarily mean more micelle formation.

We also studied two other solvents, *viz.*, *cyclo*hexane and bromoform, by the cryoscopic method. In these the solubility of the more polar detergent is much less than that in benzene. (Ethylene dibromide, a solvent of similar type, did not give solutions of suitable concentration.) The results are given in Table 2. *cyclo*Hexane behaves very similarly to benzene and so the conclusions for benzene solutions are confirmed. Bromoform also qualitatively shows the same behaviour as does benzene : the mixture effect is found here also, and the mixture does not show any perceptibly higher micelle formation, and thus the general conclusions are confirmed.

A radical departure from the existing micellar theory is needed to understand the varied aspects of solubilization : it is quite likely that these are not ascribable to a common mechanism, but it seems that the associating tendency of some molecules with molecules containing complementary groups lies at the root of all types of solubilization phenomena. The strong micelle-forming and solubilizing power of soap molecules is ascribable to the inherent tendency of soap molecules to associate either with themselves or with other types of molecule, and it is more logical to regard micelle formation and solubilization as parallel phenomena arising out of a common origin rather than to regard the latter as being caused by the former, as has been done by almost all workers in this field.

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Fluorene Analogues of Triphenylmethane Dyes ; Calculation of their Light Absorption by the Molecular-orbital Method.

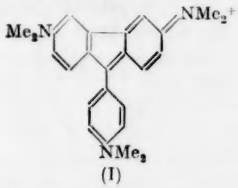
By D. A. BROWN and M. J. S. DEWAR.

[Reprint Order No. 4889.]

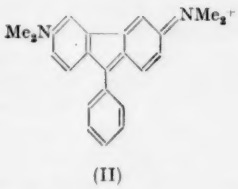
Barker and Barker (*J.*, 1954, 1307) observed remarkable bathochromic shifts in typical triphenylmethane dyes on ring-closure to fluorene derivatives. Calculation of the light absorption of these compounds by the L.C.A.O. molecular-orbital method shows that these shifts can be ascribed quantitatively to the effect of forming the additional C–C bonds. There is no need to postulate non-planarity in the fluorene ring.

BARKER and BARKER (*J.*, **1954**, **1307**) recently prepared the fluorene analogue (I) of crystal-violet, and the two fluorene analogues (II and III) of malachite-green; in each case the fluorene analogue absorbs at much lower frequencies than does the parent triphenylmethane dye. These bathochromic shifts seem at first sight too large to be due merely to the formation of one additional C–C bond, and might therefore be taken as evidence that the fluorene ring is non-coplanar, an idea which has been put forward recently by various workers on other grounds. An alternative—and opposite—explanation would be that the fluorene ring *is* coplanar, and consequently that in the fluorene dyes a coplanar

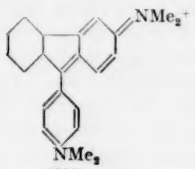
diphenylmethane system is present; whereas examination of models shows that the benzene rings in crystal-violet must be twisted well out of the general plane of the molecule, the angle of twist probably being at least 40°. Conjugation of the rings with the central carbon atom would then be more efficient in the fluorene analogue, and this might have a bathochromic effect.



(I)



(II)



(III)

To distinguish between these possibilities we calculated the light absorption of planar forms of the dyes (I), (II), and (III), and of their triphenylmethane analogues, and so obtained a quantitative estimate of the effects of the additional bonds.

It has been shown that the light absorption of basic dyes can be treated quite satisfactorily by the simple L.C.A.O. M.O. Method (Dewar, *J.*, 1950, 2329), even some of the excited levels being predicted quite accurately. In the case of the fluorene analogues of (I), (II), and (III), which are the non-alternant analogues of their parent alternant compounds, the same simplifying factors should be present: a small singlet–triplet separation, and a tendency for the π-electrons to accumulate on the terminal hetero-atoms.

The previous calculations of the absorption bands of the parent compounds crystal-violet and malachite-green were repeated and fair agreement was obtained with the previous results. However, in Table 1 the absorption previously calculated for 3680 Å has been omitted since this arises from a forbidden transition with the electric vector perpendicular to the plane of the rings; the absence of such a band in the observed spectrum is therefore not surprising. For malachite-green the calculated direction of the electric vector agrees with the experimental value for the first absorption band only if it is assumed that configurational interaction occurs between the symmetrical and the anti-symmetrical bonding orbitals at $-0{\cdot}5043$ and $-0{\cdot}5378\beta$ respectively, and this assumption seems probable in view of the closeness of these levels. The predicted directions of the electric vectors for the two observed transitions are mutually perpendicular. This agrees with the experimental determination by Lewis and Bigeleisen (*J. Amer. Chem. Soc.*, 1943, **65**, 2102) based on a direct study of the polarised fluorescence of malachite-green. Such experiments do not provide a unique assignment of the electric vector to a given band. They can only establish the mutual perpendicularity of two bands. Consequently the disagreement in Table 1 may be incorrect.

TABLE 1.

Compound	$\lambda_{max.}$ (calc.)	$\lambda_{max.}$ (obs.)	Compound	$\lambda_{max.}$ (calc.)	$\lambda_{max.}$ (obs.)
Crystal-violet	5660 (*x*, *y*)	5910 (*x*, *y*)	Malachite-green ...	6220 (*y*)	6200 (*x*)
	3300 ,,	5450 ,,		5900 (*x*)	—
	2600 ,,	3050 ,,		3470 (*x*)	4200 (*y*
		2500 ,,			

TABLE 2.

Compound	$\lambda_{max.}$ (calc.)	$\lambda_{max.}$ (expt.)	Compound	$\lambda_{max.}$ (calc.)	$\lambda_{max.}$ (expt.)
Fluorene analogue of crystal-violet (I) ...	* 8380 (*y*)	8500	Fluorene analogue of malachite-green (II)	8070 (*x*)	8500
	* 6060 (*x*)	6500		—	9540
				5590 (*y*)	5070

* The calculated $\lambda_{max.}$ have been corrected for the difference between experiment and calculation of the F.F.A.B. of crystal-violet.

For the fluorene analogues (I) and (II), any strain present in the additional bond was ignored, and it was treated simply as a normal aromatic bond. A number of experimental facts seem to support this assumption, as will be noted later. The results of these calculations are compared with experiment in Table 2. The agreement is satisfactory and

suggests that the whole difference between the triphenylmethane and fluorene dyes can be ascribed to the extra C–C bonds in the latter. The effect of these is evidently far greater than intuition might have suggested, and affords ample explanation of the observed shifts.

The fine structure of these bands is worthy of comment. For compound (II) the first absorption band exhibits a well-defined fine structure with a frequency separation of 1280 cm.$^{-1}$. Such a fine structure is common in the para- or L_b-bands of polyacenes, which show a regular vibrational structure with spacing in the region 1100—1500 cm.$^{-1}$. This may be attributed, in the absence of a complete vibrational analysis, to the fundamental and the overtones of a single vibration in each case. For the fluorene analogue the vibration responsible for the vibrational fine structure is probably the symmetric C–C vibration of the extra bond. Consequently, the spacing of 1280 cm.$^{-1}$, which is intermediate between that of the single and the double bond, lends further support to the assumption that this bond is largely aromatic in character. The fluorene analogue of crystal-violet (I) possesses a very wide band at approximately 8500 Å, indicating that the vibrational fine structure is obscured by solvent interaction.

It appears at first sight from the experimental absorption curves (Barker and Barker, *loc. cit.*) that the fluorene compounds absorb more weakly than do the triphenylmethane analogues. However, it is the oscillator strength or the integrated band intensity which is the correct measure of the intensity of absorption (Mulliken, *J. Chem. Phys.*, 1939, **7**, 14) and in this case the lower values of $\varepsilon_{max.}$ for the fluorenes are compensated by the greater width of the maxima. The integrated band intensities are actually similar in both the parent dyes and their fluorene analogues.

It has been assumed so far that all the C–C resonance integrals have the same value; this is equivalent to neglecting any possible effects of non-coplanarity in the triphenylmethane derivatives. However it has been shown both theoretically and experimentally (Dewar, unpublished work) that the effect of non-coplanarity on the light absorption of such dyes is in fact small. It is very much smaller than the effects that are being considered here. In any case these effects could not possibly be due to such non-coplanarity for the effect of non-coplanarity is *bathochromic*; increasing the coplanarity of a triphenylmethane dye actually has a hypsochromic effect.

We also tried to calculate the differences in light absorption between the analogous diphenylmethane and fluorene derivatives by a perturbation method, regarding the formation of the extra bond in the latter as the perturbation. Although the calculated spectral shifts were in the right direction they were very much smaller than those observed. This is surprising since analogous perturbation methods have proved very successful in other cases; and it suggests that the large bathochromic displacements are not directly due to the formation of the extra bond. It seems likely that the main effect is due to the radical change in charge distribution that occurs when the alternant conjugated system of the diphenylmethane is converted into a non-alternant fluorene structure (cf. Coulson and Rushbrook, *Proc. Camb. Phil. Soc.*, 1940, **36**, 193). This factor was neglected in our first-order perturbation treatment.

Method.—This was quite standard. The L.C.M.O. method (Dewar, *ibid.*, 1949, **45**, 639) was employed for the parent compounds since these can be treated very simply by it and much labour is thereby saved.

Overlap was neglected since the aim of the calculations was comparative; likewise no allowance was made for the inductive effect of the hetero-atoms.

The following values were assigned to the Coulomb term (α) of an atom relative to carbon and to the resonance integrals (β) : α_N (in NR_3) = β_{CC}; β_{CN} = β_{CC}; β_{CC} = 73·2 kcals.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, December 15th*, 1953.]

Steroidal Alkaloids. Part II. Some Observations on the Constitution of Cevine.*

By D. H. R. Barton, C. J. W. Brooks, and J. S. Fawcett.

[Reprint Order No. 5057.]

Treatment of " anhydrocevine " (cevine orthoacetate) with periodic acid affords a crystalline aldehydo-γ-lactone, thus confirming the masked α-ketolic character of cevine.

Acetylation of cevine with hot pyridine–acetic anhydride gives a crystalline triacetate which is stable to chromic acid, thus proving that the α-glycol system of cevine is ditertiary.

The ready interconversion of cevine and " anhydrocevine " tetra-acetates has been demonstrated. The two compounds come to equilibrium with each other at room temperature in solvents containing acetic acid. The " anhydro "-compounds of cevine and its derivatives have been shown to be orthoacetates. The kinetics of orthoacetate formation in the cevine tetra-acetate system have been elucidated and mechanistic proposals have been entertained.

In Part I * of this series the functional groups of the steroidal alkamine, cevine, $C_{27}H_{43}O_8N$, were classified as follows. Three oxygen atoms bound in a masked α-ketol system (I; R = R′ = H); † two oxygen atoms present as a ditertiary or tertiary-(sterically hindered)secondary α-glycol, and one oxygen atom present as an easily esterified primary or secondary hydroxyl group; the remaining two oxygen atoms are classified as tertiary hydroxyl groups. The absence of an ethylenic linkage and the heptacyclic character of the molecule were demonstrated. Our attention has now been turned to a more detailed examination of the complex chemistry of cevine.

Our efforts were first directed to verification of the presence of the grouping (I; R = R′ = H). Reduction of cevine by sodium and alcohol gives, besides dihydrocevine, a deoxydihydrocevine (Jacobs and Craig, *J. Biol. Chem.*, 1938, **125**, 625). The loss of one hydroxyl group is nicely accounted for by the α-ketolic formulation (cf. Macbeth and Robertson, *J.*, 1953, 3512).

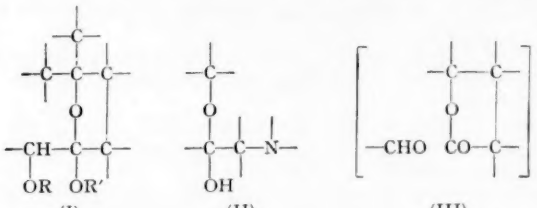
Many of the experimental facts previously discussed are compatible with an alternative masked tertiary α-amino-ketone formulation as in (II). This must be rejected on the following grounds. Whilst the tertiary α-amino-ketone *N*-acetonylpiperidine reduced Fehling's solution and consumed 1 mol. of lead tetra-acetate, its methiodide had no reducing power and consumed no significant amount of lead tetra-acetate. Cevine methiodide, on the other hand, retained intact the reducing power of cevine and, like cevine, consumed 2 mols. of lead tetra-acetate almost instantaneously. Clearly the masking of the nitrogen atom of cevine by quaternisation has no effect on those properties of the molecule which we have ascribed (Barton and Eastham, *loc. cit.*) to the presence of the masked α-ketol system.

The partial structure (I; R = R′ = H) was finally confirmed as follows (see also Barton and Brooks, *Chem. and Ind.*, 1953, 1366). " Anhydrocevine " (cevine ortho-acetate, see below) (Stoll and Seebeck, *Helv. Chim. Acta*, 1953, **36**, 189) in which the ditertiary α-glycol system (see further below) is protected against glycol cleavage, consumed 1 mol. of periodic acid, to give a nicely crystalline compound (III). This was characterised by its infra-red spectrum (in chloroform) as a γ-lactone (band at 1770 cm.$^{-1}$)

* Part I, *J.*, 1953, 424.

† In partial formula (I) we have formed the ether bridge of cevine from a tertiary hydroxyl, not from a secondary hydroxyl, group as in the paper by Barton and Eastham (Part I). The reason for the change is that " anhydrocevagenin triacetate " is now recognised as cevagenin orthoacetate diacetate (see below), and we find that it is stable to chromic acid. It cannot therefore retain an unacetylatable secondary hydroxyl group. These experiments, carried out in collaboration with Dr. P. de Mayo, will be published in the near future.

and as an aldehyde (bands at 1724 and 2730 cm.$^{-1}$). The presence of the carbonyl group was substantiated by the preparation of a 2 : 4-dinitrophenylhydrazone. This retained the γ-lactone band (in chloroform) at 1775 cm.$^{-1}$, but had lost the bands indicative of the aldehyde function. Further, the ultra-violet absorption maximum was characteristic of that of an aldehyde derivative (see Braude and Jones, *J.*, 1945, 498). The cleavage



(I) (II) (III)

product showed reducing power towards Fehling's solution in consonance with its aldehydic nature.

Additional evidence for the masked α-ketolic structure of cevine has been provided by Sundt, Jeger, and Prelog (*Chem. and Ind.*, 1953, 1365) and by Stoll, Stauffacher, and Seebeck (*Helv. Chim. Acta*, 1953, **36**, 2027), who oxidised the α-ketol cevagenin (see Barton and Eastham, *loc. cit.*) to the corresponding diosphenol.

Treatment of cevine under mild acetylating conditions affords a diacetate (I; R = Ac, R′ = H) (see Barton and Eastham, *loc. cit.*). We now find that when cevine is heated on the steam-bath with pyridine–acetic anhydride it affords a crystalline triacetate which we formulate as (I; R = R′ = Ac). There is sound analogy (Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252) for the preferential acetylation of the tertiary hydroxyl group attached to the carbon bearing the ethereal oxygen atom (relative to the other tertiary hydroxyl groups). The triacetate retained the α-glycol system of cevine for it consumed 1 mol. of lead tetra-acetate and of periodic acid. It was, however, resistant to chromic acid oxidation and therefore a first proof is provided that the α-glycol system of cevine is indeed ditertiary.

We now turn to a consideration of the nature of " anhydrocevine " (see also Barton and Fawcett, *Chem. and Ind.*, 1953, 615). Treatment of cevadine with acetic anhydride and perchloric acid gives " triacetylanhydrocevadine " (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1942; Kupchan, Lavie, Deliwala, and Andoh, *J. Amer. Chem. Soc.*, 1953, **75**, 5519) whilst cevagenin affords " triacetylanhydrocevagenin " under analogous but not identical conditions (Stoll and Seebeck, *loc. cit.*). The last authors showed that the " anhydro "-compounds were produced with disappearance of the (ditertiary) α-glycol system and regarded them as formed by the change

Stoll and Seebeck (*loc. cit.*) also drew attention to the fact that comparable acetylation of cevine itself gave cevine tetra-acetate, and not an " anhydro "-compound. It seemed to us that this difference might be of structural significance and that it justified a further examination of " anhydro "-compound formation. We soon found that " anhydrocevine tetra-acetate " previously obtained by Stoll and Seebeck (*Helv. Chim. Acta*, 1953, **36**, 189) by an indirect route from veracevine * (Pelletier and Jacobs, *J. Amer. Chem. Soc.*, 1953, **75**, 3248; Kupchan *et al.*, *loc. cit.*) is, in fact, the direct product of perchloric acid-catalysed

* We thank cordially Dr. S. M. Kupchan (Harvard) for informing us that he intends to withdraw his name protocevine for this compound and to use instead the name veracevine proposed by Pelletier and Jacobs. Dr. Kupchan has also kindly informed us of experiments on veracevine triacetate which parallel those reported by us on cevine triacetate (see Kupchan and Lavie, *J. Amer. Chem. Soc.*, 1954, **76**, 314).

acetylation, and that cevine tetra-acetate itself is formed by ready hydration during crystallisation from aqueous acetic acid. Further investigation revealed that both cevine tetra-acetate and its " anhydro "-derivative and their respective perchlorates came into equilibrium with each other in aqueous acetic acid at room temperature. In pure acetic acid the equilibrium is 100% on the side of the " anhydro "-compound, in water it is 100% on the side of the cevine tetra-acetate. Illustrative data for the equilibrium of the perchlorates at 28·2° in mixtures of acetic acid and water are summarised in Table 1. Most of the results were, for convenience, obtained by starting with cevine tetra-acetate

TABLE 1.

Acetic acid (%, v/v)	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	" Anhydro " (ortho-acetate) derivative (%) at equil.*	Acetic acid (%, v/v)	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	" Anhydro " (ortho-acetate) derivative (%) at equil.*
100	+118°	1·14	100	60	+54·5	1·21	23·0
95	+ 95·5	1·49	72·5	50	+53	3·27	21·2
90	+ 82	1·10	56·5	30	+49	2·01	16·5
85	+ 73	1·36	45·5	20	+46	0·95	12·7
80	+ 64·5	1·62	35·0	0	+35·5 †	0·20	0
70	+ 61	3·38	31·0				

* The composition of the equilibrium mixture is calculated on the basis of $[\alpha]_D$ +118° for " anhydrocevine tetra-acetate " (cevine orthoacetate triacetate) perchlorate and +35·5° for cevine tetra-acetate perchlorate.

† Determined in 4-dm. tube ; the other rotations were taken in 1-dm. tubes.

perchlorate but appropriate check determinations were run starting with the " anhydro "-compound.

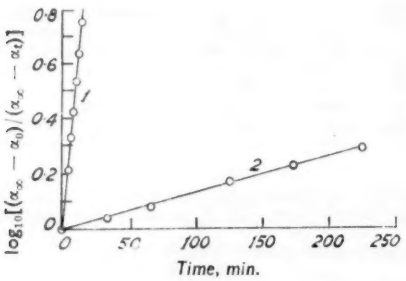
The analytical data of Stoll and Seebeck (*loc. cit.*) disclosed that the " anhydro "-compounds are indeed formed by dehydration. The dependence of the equilibrium data summarised in Table 1 on the water content of the medium confirms this conclusion. It seemed to us, however, that the " anhydro "-compounds were more likely to be tetrahydrofuran or pyran derivatives (see Barton and Fawcett, *loc. cit.*) or even orthoacetates, than epoxides. The possibility of an orthoacetate formulation was strengthened by a comparative study of the infra-red spectra of cevine tetra-acetate and " anhydrocevine tetra-acetate." In chloroform solution it was found that the strength of the acetate band at 1734 cm.$^{-1}$ was only about 75% as intense for the " anhydro "-compound as for cevine tetra-acetate. Further, the infra-red spectrum of " anhydrocevine tetra-acetate " showed a significantly displaced " methyl " band at 1397 cm.$^{-1}$, which band is present for ethyl orthoacetate (at 1392 cm.$^{-1}$ in carbon tetrachloride solution) and other " anhydro "-compounds of cevine, but absent for other cevine derivatives. In addition " anhydrocevine tetra-acetate " has a complex series of ether bands near 1140 cm.$^{-1}$ which is also present in the ethyl orthoacetate spectrum.

The correctness of the orthoacetate formulation was finally proved by a study of " anhydrocevine." In the infra-red spectrum of its carbon tetrachloride solution this compound shows no acetate band, but possesses the displaced " methyl " band at 1404 cm.$^{-1}$ and the complex ether bands near 1140 cm.$^{-1}$. Analytical data disclosed the formula $C_{29}H_{43}O_8N,CH_3{\cdot}OH$ and were not in agreement with earlier findings by Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942) which suggested a formula $C_{27}H_{41}O_7N$. The equivalent weight of " anhydrocevine " was in excellent agreement with the new formula. Finally acetyl determinations revealed the presence of one " acetyl " group, confirmed by the characterisation of the acetic acid as its *p*-bromophenacyl ester—cevine, itself, gave no volatile acid under the conditions of the acetyl determination. In the Kuhn–Roth *C*-methyl determination cevine showed an average of 5·8% of *C*-methyl groups and " anhydro-cevine " an average of 8·2%, again in agreement with the orthoacetate formulation. Our findings require the following nomenclature changes (new name in parentheses) : " anhydrocevine " (cevine orthoacetate) ; " anhydrocevine tetra-acetate " (cevine orthoacetate triacetate) ; " anhydrocevagenin triacetate " (cevagenin orthoacetate diacetate) ; and so on.

The large rotational shift accompanying orthoacetate formation makes this reaction

well suited to kinetic analysis. In pure acetic acid the dehydration of cevine tetra-acetate to cevine orthoacetate triacetate is quantitative and follows first-order kinetics up to at least 70% conversion. Illustrative data are plotted in the Figure. Reproducibility was satisfactory as shown by appropriate repetitions. Preliminary experiments in aqueous acetic acid indicated that in this medium the two compounds came into equilibrium by reversible first-order reactions, but we have not made an extensive investigation.

The conversion of cevine tetra-acetate perchlorate into the corresponding orthoacetate in acetic acid containing 20% v/v of acetone has also been studied. This change is likewise of the first order (cf. Figure). It was remarkable that the perchlorate reacted about



1, *Cevine tetra-acetate in acetic acid at* 28·2°.
2, *Cevine tetra-acetate perchlorate in* 80% *v/v acetic acid–acetone at* 28·2°.

60 times *slower* than the parent base. This observation stimulated us to examine the effect of perchloric acid and of triethylamine. Both compounds catalysed orthoacetate formation in proportion to the amount added (see Table 2; measurements were at 28·2° in pure acetic acid).

TABLE 2.

Concn. (g./100 ml.)	Concn. (x) of catalyst	$10^3 k$ (min.$^{-1}$)	$10^3(k - k_0)/x$	Concn. (g.100 ml.)	Concn. (x) of catalyst	$10^3 k$ (min.$^{-1}$)	$10^3(k - k_0)/x$
Perchlorates.				*Free bases.*			
1·63	0·0 *	2·95 (k_0)	—	1·63	0·0	122 (k_0)	—
1·34	0·023 †	164	7000	1·54	1·0 ‡	166	44
1·54	0·047	300	6300	1·53	2·0	209	43·5
				1·52	3·0	256	43·5
				1·66	5·0	348	45

* Value for reaction in acetic acid containing 20% of dry acetone: the equilibrium point lies at 97·5% of complete reaction and so does not affect the simple first-order kinetics.
† G./100 ml. ‡ Ml./100 ml. of solution.

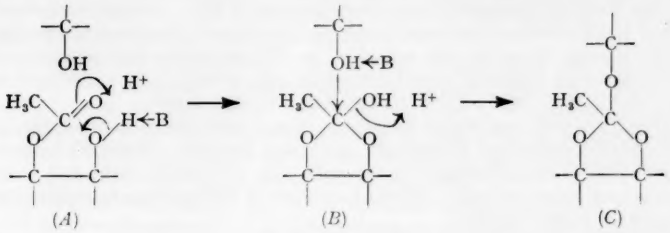
The variation of rate of orthoacetate formation with temperature has been studied for cevine tetra-acetate (Table 3). The results gave a straight-line activation energy plot from which it can be calculated that $k = 9{\cdot}1 \times 10^{10}\, e^{-16{,}400/RT}$ min.$^{-1}$ for the formation of cevine orthoacetate triacetate in pure acetic acid. The results at each temperature were closely duplicated in repetitions.

TABLE 3.

Temp.	$[\alpha]_D$ at equil.	Concn. (g./100 ml.)	Orthoacetate (%) at equil.	$10^3 k$ (min.$^{-1}$)
28·2°	+127°	1·63	100	122
33·5	+127	1·45	100	198
39·0	+127·5	1·59	100	314

The catalytic action of acid and base (cf. Swain and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2538) on the rate of orthoacetate formation and the observed kinetic effects can be reconciled with a mechanism such as that annexed (B = base). At the present time we cannot distinguish the rate-determining step. Either (A) and (B) must be in equilibrium and (B) ⟶ (C) is rate-determining; or (A) ⟶ (B) is slow relative to (B) ⟶ (C). The assignment of a definite mechanistic role to the base explains the otherwise curious fact that

the perchlorate reacts so much more slowly (as there is no free tertiary amine) than the free base.



Experimental

For general experimental details see *J.*, 1953, 424. Unless specified to the contrary, rotations were determined in chloroform solution at room temperature and light absorption maxima in ethanol (with a Unicam S.P. 500 Spectrophotometer). Infra-red spectra were kindly determined by Messrs. Glaxo Laboratories Ltd. in carbon disulphide solution except as otherwise stated. Acetyl determinations were carried out according to H. Roth, Pregl's "Quantitative Organic Microanalysis," J. and A. Churchill Limited, London, 1937.

Deoxydihydrocevine.—Cevine was reduced with sodium and ethanol (instead of *n*-butanol) according to the directions of Jacobs and Craig (*J. Biol. Chem.*, 1938, **125**, 625). Isolation of the product by chloroform extraction (cf. *idem, loc. cit.*) and concentration of the chloroform solution gave deoxydihydrocevine (10—25%), m. p. 276—278°, $[\alpha]_D$ −18° (*c*, 1·98 in MeOH) (Found: C, 65·0; H, 9·25. Calc. for $C_{27}H_{45}O_7N$: C, 65·4; H, 9·15%). Evaporation of the mother-liquors and crystallisation from methanol furnished dihydrocevine (15—20%).

Confirmatory Tests for the α-Ketolic Structure of Cevine.—Cevine, cevine orthoacetate, cevine methiodide, and *N*-acetonylpiperidine (kindly supplied by Dr. R. C. Cookson) all gave strongly positive reducing tests with Fehling's solution. *N*-Acetonylpiperidine methiodide (Stoermer and Burkert, *Ber.*, 1895, **28**, 1250) was non-reducing.

Lead tetra-acetate titrations were carried out according to the procedure described in Part I (*loc. cit.*). The uptake in mols. of oxidant after 5 min. was: cevine, 1·95; cevine methiodide, 1·98; cevine tetra-acetate methiodide, <0·2; *N*-acetonylpiperidine, 0·96; *N*-acetonylpiperidine methiodide, 0·04.

Cevine Tetra-acetate.—The perchlorate (Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1270) had (from aqueous acetic acid) $[\alpha]_D$ +38° (*c*, 0·95 in MeOH), +35° (*c*, 1·18 in acetone). The two forms of this compound described in Part I are the true cevine tetra-acetate perchlorate (lower m. p.) and cevine orthoacetate triacetate perchlorate (higher m. p., see below). The derived cevine tetra-acetate had m. p. 295—297° (decomp.), $[\alpha]_D$ +22° (*c*, 2·05), +37° (*c*, 2·10 in MeOH), +35° (*c*, 0·84 in acetone), +36° (*c*, 1·10 in EtOH).

Cevine Orthoacetate Triacetate.—Cevine tetra-acetate perchlorate (500 mg.) in "AnalaR" acetic acid (10 ml.) was heated on the steam-bath for 10 min. Concentration *in vacuo* gave *cevine orthoacetate triacetate perchlorate* (400 mg.), m. p. (from acetic acid) 268—269° (decomp.), $[\alpha]_D$ +109° (*c*, 0·95 in MeOH; unchanged for 24 hr.), +118° (*c*, 0·71 in acetic acid) (Found: C, 53·95, 54·35; H, 6·55, 6·95; N, 1·95; Cl, 3·8; Ac, 26·6. $C_{35}H_{49}O_{11}N,HClO_4,CH_3{\cdot}CO_2H$ requires C, 54·15; H, 6·65; N, 1·7; Cl, 4·35; Ac, 26·2%). Recrystallisation of this perchlorate from 1 : 2 acetic acid–water gave cevine tetra-acetate perchlorate (see above), identified by m. p., mixed m. p., and rotation.

Treatment of cevine orthoacetate triacetate perchlorate (see above) in acetone–ether with cold dilute aqueous ammonia gave the parent base, m. p. [from carbon tetrachloride–light petroleum (b. p. 60—80°)] 282—284° (decomp.), $[\alpha]_D$ +111° (*c*, 0·97), +127° (*c*, 1·14 in acetic acid) (Found: C, 63·9, 64·1; H, 7·75, 7·55; N, 2·65; Ac, 27·2, 24·6. Calc. for $C_{35}H_{49}O_{11}N$: C, 63·7; H, 7·5; N, 2·1; Ac, 26·1%).

Cevine Orthoacetate ("*Anhydrocevine*").—This compound was prepared from cevine orthoacetate triacetate by alkaline hydrolysis essentially according to the procedure of Stoll and Seebeck (*Helv. Chim. Acta*, 1952, **35**, 1942) for the hydrolysis of cevadine orthoacetate diacetate. *Cevine orthoacetate* had m. p. (colourless prisms from methanol) 180—190° and 245—250°, $[\alpha]_D$ +62°, +62°, +62°, +62° (*c*, 1·05, 1·03, 1·08, and 1·04; all in EtOH) [Found, in sample dried *in vacuo* at 95° for 2 days (no change in wt. or crystal form): C, 63·45, 63·5;

H, 8·4, 8·25; Ac, 8·05, 7·25; *C*-Me, 7·9, 8·5%; equiv. (determined potentiometrically), 566. $C_{29}H_{43}O_8N,CH_3{\cdot}OH$ requires C, 63·7; H, 8·4; Ac, 7·6; 3*C*-Me, 8·0; 4*C*-Me, 10·6%; equiv., 566]. On being dried at 160°/0·01 mm. for 5 hr. the crystals sintered and lost 5·5% of their weight (the solvated formula given above requires 5·7%). In one acetyl determination the volatile acid was isolated as the sodium salt and converted into the *p*-bromophenacyl ester, identified as the acetate by m. p. and mixed m. p. When cevine was subjected to an acetyl determination it gave an apparent acetyl content of only 0·26%. Cevine gave 4·8 and 6·75% of *C*-Me (Calc. for $C_{27}H_{43}O_8N,3{\cdot}5H_2O$: 2*C*-Me, 5·25; 3*C*-Me, 7·85%).

In order to confirm that the cevine orthoacetate was solvated with methanol, 50 mg. were oxidised with acidified potassium dichromate and steam-distilled. Formaldehyde was detected in the distillate by the colour reaction with chromotropic acid and by formation of the dimedone derivative (m. p. and mixed m. p.). Similar oxidation of the orthoacetate after drying at 160° (see above) gave no formaldehyde.

Periodic Acid Oxidation of Cevine Orthoacetate.—The orthoacetate (660 mg.) in ethanol (20 ml.) was treated with aqueous periodic acid (30 ml.; M/20), and the solution made up to 50 ml. with ethanol. The uptake (1·00 mol.) of periodic acid was essentially instantaneous (<10 min.). In repeat experiments the amount of periodic acid consumed (10-min. titration; no further uptake after 60 min.) was 0·99 and 0·99 mol. For working up, excess of aqueous sodium arsenite solution and 20 ml. of saturated aqueous sodium hydrogen carbonate were added and the solution was extracted with chloroform (6 × 25 ml.). Evaporation *in vacuo* afforded a colourless oil which crystallised slowly from chloroform–ethyl acetate–light petroleum (b. p. 60—80°) in a flask open to the air, to give prisms of the *aldehydo-γ-lactone* (415 mg.), m. p. 230—233° (decomp.), $[\alpha]_D$ ±0° (*c*, 0·65) (Found: C, 61·75, 61·65, 61·65; H, 7·45, 7·6, 8·2; N, 2·5; Ac, 6·05%; equiv., 575. $C_{29}H_{41}O_8N,2H_2O$ requires C, 61·35; H, 8·0; N, 2·45; Ac, 7·6%; equiv., 568).

The corresponding 2 : 4-*dinitrophenylhydrazone* formed yellow crystals [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 210° after preliminary sintering, $\lambda_{max.}$ 355 mμ (ε 24,000 in $CHCl_3$) (Found: N, 10·6. $C_{35}H_{45}O_{11}N_5$ requires N, 9·85%).

The corresponding *oxime*, prepared with pyridine–hydroxylamine hydrochloride at room temperature, had m. p. 220—225° (decomp.) [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: N, 4·45. $C_{29}H_{42}O_8N_2$ requires N, 5·1%).

Cevine Triacetate.—Cevine (200 mg.) in pyridine (2 ml.) and acetic anhydride (4 ml.) was heated on the steam-bath for 2 hr. The excess of reagents was removed *in vacuo* and the residue dissolved in a little water, made basic with ammonia, and extracted with chloroform. Evaporation of the chloroform *in vacuo* and crystallisation from ether–light petroleum (b. p. 60—80°) gave *cevine triacetate* (needles; 124 mg.), m. p. 307—308° (decomp.), $[\alpha]_D$ +19°, +19° (*c*, 1·74, 1·70 in acetone) (Found: C, 62·2; H, 7·8; N, 2·1, 2·3; Ac, 20·8. $C_{33}H_{49}O_{11}N$ requires C, 62·35; H, 7·75; N, 2·2; Ac, 20·3%). The triacetate (9·8 mg.) in acetic acid (10 ml.) containing lead tetra-acetate (4 mols.) was left at room temperature for 10 min. The uptake of oxidant was 0·95 mol., unchanged for a further 18 hr. The same result (0·97 mol. uptake) was observed in 80% aqueous acetic acid. The triacetate (100 mg.) in ethanol (10 ml.) was treated with excess of periodic acid solution (10 ml.) and saturated sodium hydrogen carbonate solution (5 ml.) for 10 min. The periodic acid uptake corresponded to 1·00 mol. and was unchanged on further standing (experiment by Dr. P. de Mayo).

Cevine triacetate (138 mg.) treated with acetic anhydride–perchloric acid as in the acetylation of cevine itself (see above) gave, after crystallisation from aqueous acetic acid, cevine tetra-acetate perchlorate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +32° (*c*, 1·16 in acetone)}.

Cevine triacetate (94 mg.) was hydrolysed with 20% ethanolic potassium hydroxide as in the preparation of cevine (Macbeth and Robinson, *J.*, 1922, **121**, 1571). The product (62 mg.), crystallised from aqueous ethanol, was identified as cevine by m. p., mixed m. p., and rotation {$[\alpha]_D$ −17° (*c*, 1·04 in EtOH)}.

The triacetate (39·6 mg.) in 95% aqueous acetic acid (10 ml.) containing 125% of the theoretical amount of chromic acid for the oxidation of 1 secondary hydroxyl group was left overnight at room temperature. There was no consumption of oxidant (titration) and pure triacetate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ +20° (*c*, 1·07 in acetone)}, was recovered unchanged in 70% yield.

Tests for Orthoacetate Formation and its Reversal.—The following compounds, under the conditions stated below, did not afford orthoacetates at room temperature, as shown by the constancy of their rotations after 20 hr. Initial and final rotations are given sequentially. All

rotations are in acetic acid unless specified otherwise. Cevine: −18°, −17° (*c*, 1·22); cevine diacetate, +8°, +6° (*c*, 1·01); cevine triacetate, +27°, +27° (*c*, 1·72); cevine tetra-acetate (see text), also +22° (*c*, 2·05 in $CHCl_3$), +35°, +36° (*c*, 0·84 in acetone), +46°, +45° (*c*, 0·76 in acetone containing 10·1% w/v of triethylamine and 6·0% w/v of acetic acid, thus giving a molecular ratio of triethylamine : acetic acid of 1 : 1).

Kinetics of Orthoacetate Formation.—The course of the reaction was followed by using a 2-dm. polarimeter tube fitted with a water jacket, which was connected to a circulating pump supplying water from a thermostatically controlled water-tank. The polarimeter tube, placed in a Hilger Standard Polarimeter, soon attained constant temperature, which was measured in a trial experiment for each temperature setting and checked at the end of each experiment. In this way the temperature could be controlled within ±0·05°.

The determinations were carried out by rapidly dissolving 50—100 mg. of compound in 5 ml. of solvent (previously warmed to the appropriate temperature) and measuring rotations at suitable time intervals.

Reaction rates were calculated from straight line plots of $\log_{10}[(\alpha_\infty - \alpha_0)/(\alpha_\infty - \alpha_t)]$ against t where the final rotation, α_∞, was taken after a period corresponding to 10 times the half-life.

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, January 25th*, 1954.]

The Fluorination of Organochlorodisiloxanes.

By D. S. PAYNE.

[Reprint Order No. 5116.]

The reactions of dimethyl- and diphenyl-tetrachlorodisiloxanes and a series of ethylchlorodisiloxanes with ammonium fluoride are described.

MONOETHYL-, diethyl-, triethyl-, and dimethyl-chlorodisiloxanes react with ammonium fluoride yielding, by fission of the Si–O–Si linkage, polymeric material together with monosilane derivatives. The tetraethyl- and pentaethyl-chlorodisiloxanes under similar conditions yield only the corresponding ethylfluorodisiloxanes and diphenyltetrachlorodisiloxane gives a non-volatile resin.

The mild exchange of chlorine for fluorine in covalent halides is readily achieved by ammonium fluoride (Wilkins, *J.*, 1951, 2726). With hexachlorodisiloxane and with hexachlorodisilane under these conditions the Si–O–Si and Si–Si bonds break to yield monosilane derivatives. Hexachlorodisilane undergoes a similar fission with ammonium chloride or trimethylamine hydrochloride. Diethyltetrachlorodisilane reacts with ammonium chloride to yield a mixture of monoethyl- and diethyl-chlorosilanes; the analogous fission of diethyltetrachlorodisiloxane with ammonium fluoride, however, gives exclusively (in up to 90% yield) monoethyltrifluorosilane but no diethyldifluorosilane. These results served to identify the diethyltetrachlorodisiloxane obtained by the reaction of ethylmagnesium bromide with hexachlorodisiloxane as the symmetrical 1 : 2-isomer (Emeléus and Payne, *J.*, 1947, 1590). Triethyltrichlorodisiloxane similarly gives no triethylfluorosilane but yields a mixture of monoethyl- and diethyl-fluorosilanes, and is thus the 1 : 1 : 2-compound rather than the 1 : 1 : 1. The existence of only one of the possible isomers of the diethyl, triethyl, and tetraethyl derivatives is supported by the sharp boiling points of these compounds found during their preparation. Reaction in ether solution between ethylmagnesium bromide and hexachlorodisiloxane or its alkyl derivatives thus occurs exclusively at the chlorine atom attached to the least alkylated (*i.e.*, the least electronegative) silicon atom. Hexachlorodisilane under the same conditions gives a mixture

of isomers indicating that reaction occurs at both silicon atoms, although even in this case reaction at the less electronegative silicon atom is the more likely (Wilkins, *loc. cit.*).

The fission reaction with ammonium fluoride is highly exothermic and does not appear to occur below a threshold temperature characteristic of the type of compound, which is 130° for ethylchlorodisiloxanes, and below room temperature for dimethyltetrachlorodisiloxane. Anhydrous hydrogen fluoride attacks the alkylchlorodisiloxanes similarly giving monosilane derivatives and a small amount of polymeric material. Here the attack on the Si–O–Si linkage is extended to the polymeric material which is one of the products of the reaction with ammonium fluoride, leading to almost complete conversion into fluorosilane derivatives.

It seems likely that the fission reaction proceeds by the attack of hydrogen fluoride derived from the ammonium fluoride by thermal dissociation on the Si–O–Si linkage, leading to the formation of Si–F and Si–OH groups, the latter undergoing further condensation with unchanged material and with fluoro-derivatives to yield polymers. Similarly, the ammonia freed during this reaction is absorbed by the halides to give condensation products of high molecular weight. Ammonia has no effect on the Si–O–Si bond in the alkylchlorodisiloxanes, reaction leading solely to the replacement of chlorine by an amino-group and further condensation. Wilkins (*J.*, 1953, 3409) has shown that the Si–Si linkage is attacked by the ammonia obtained by dissociation of the ammonium salt, which mechanism does not appear to occur with the disiloxane linkage.

Experimental

Ammonium fluoride was dried ($CaCl_2$, CaO), and before use, in a vacuum desiccator over phosphoric oxide. Anhydrous hydrogen fluoride was obtained from a cylinder and contained *ca.* 0·5% of impurities, chiefly sulphur dioxide. The organo-chlorodisiloxanes were freshly distilled and degassed before use. Each reaction was carried out in a Pyrex flask fitted with reflux condenser and attached directly to an all-glass vacuum system for the collection and examination of the volatile products. A plug of glass wool served to retain solid materials in the flask.

The Reaction between Ammonium Fluoride and Monoethylpentachlorodisiloxane.—Monoethylpentachlorodisiloxane (0·04 mole) reacted vigorously at 130° with an excess of solid ammonium fluoride (0·4 mole). No volatile silicon compound was formed, and the residue consisted of a water-soluble mixture of ammonium chloride, fluoride, and fluorosilicate, and a water-insoluble portion which was dried at 130° (3·2 g.) [Found: C, 23·4; H, 5·9. Calc. for $(EtSiO_{1\cdot5})_n$: C, 29·6; H, 6·2%]. The reaction being assumed to proceed according to the equation:

$$Si_2OEtCl_5 \xrightarrow[130°]{NH_4F} (EtSiO_{1\cdot5})_n + nSiF_4 \longrightarrow n(NH_4)_2SiF_6$$

the yield of polymer was 100%.

The Reaction between Ammonium Fluoride and Diethyltetrachlorodisiloxane.—Diethyltetrachlorodisiloxane reacted with ammonium fluoride as shown in the following table:

$Si_2OCl_4Et_2$ used, mole	0·0175	0·0330	0·0165	0·0120
NH_4F used, mole	0·070	0·135	0·066	0·077
Mole ratio, $Si_2OCl_4Et_2 : NH_4F$	1 : 4	1 : 4	1 : 4	1 : 6·5
$EtSiF_3$, mole	0·011	0·025	0·009	0·011
Mole ratio, $EtSiF_3 : Si_2OCl_4Et_2$	0·65 : 1	0·75 : 1	0·55 : 1	0·90 : 1

The silicon-containing volatile product was ethyltrifluorosilane, together with a very small amount of a material, insufficient of which was available even after pooling the products of several experiments for complete identification, but which was possibly a partially fluorinated diethyltetrachlorodisiloxane. The residue was a white insoluble polymer and excess of ammonium fluoride. No diethyldifluorosilane or fluorochlorosilane derivative was obtained. At 120° the reaction was very slow but at 130° it proceeded vigorously, and the variation of yield was considered to be due to the difficulty of controlling it.

The Reaction between Ammonium Fluoride and Triethyltrifluorodisiloxane.—Reaction of triethyltrifluorodisiloxane (0·075 mole) and ammonium fluoride (0·4 mole) gave: a volatile mixture of ethyltrifluorosilane (0·006 mole) and diethyldifluorosilane (0·04 mole), a residue

consisting of a water-soluble portion, ammonium fluoride and chloride, and an ether-soluble fluorine-containing oil, which did not distil below 250°/10^{-3} mm. No trifluorotriethyldisiloxane or triethylfluorosilane was obtained.

The Reaction between Ammonium Fluoride and Tetraethyldichlorodisiloxane.—Tetraethyldichlorodisiloxane (0·035 mole) reacted vigorously with ammonium fluoride (0·175 mole) at 136°, a very small quantity of a volatile product being obtained, b. p. *ca.* 60° (cf. diethyldifluorosilane, b. p. 62°). *Tetraethyldifluorodisiloxane* (5·35 g., 70% yield) was obtained from the residue as a liquid, b. p. 175° (Found: C, 42·2; H, 9·1; Cl, 0. $Si_2OEt_4F_2$ requires C, 42·5; H, 8·9%). It is hydrolysed only slowly by water but more rapidly by alkalis.

The Reaction between Ammonium Fluoride and Pentaethylchlorodisiloxane.—When pentaethylchlorodisiloxane (0·05 mole) reacted with ammonium fluoride (0·135 mole) no readily volatile material was collected. *Pentaethylfluorodisiloxane* (10 g., 85% yield) was obtained from the residue as a liquid, b. p. 114—116°/43 mm. (Found: C, 49·25; H, 10·9; Cl, 0. Si_2OEt_5F requires C, 50·8; H, 10·6%). This compound is not hydrolysed by water, or cold N-sodium hydroxide, but is hydrolysed by boiling 10N-sodium hydroxide to yield the corresponding pentaethyldisiloxanol.

The Reaction between Ammonium Fluoride and Dimethyltetrachlorodisiloxane.—Dimethyltetrachlorodisiloxane (0·0575 mole) reacted with ammonium fluoride (0·3 mole) giving a large volume of volatile product, consisting of methyltrifluorosilane (0·051 mole, 90% yield) and a very small quantity of an unidentified liquid containing fluorine and chlorine. The solid residue yielded a white polymeric material (2·1 g.) [Found: C, 17·9; H, 4·2. Calc. for $(MeSiO_{1\cdot5})_n$: C, 18·0; H, 4·5%]. No evidence for the formation of dimethyldifluorosilane was obtained.

The Reaction of Ammonium Fluoride and Diphenyltetrachlorodisiloxane.—Several attempts were made to carry out this reaction, but no volatile material containing silicon was obtained and all the products were brown resins. In one experiment a small amount of benzene was collected.

THE UNIVERSITY, GLASGOW. [*Received, February 12th,* 1954.]

Stereochemical Studies. Part I. The Relative Configurations of (−)-Aminophenylacetic Acid (α-Phenylglycine) and (−)-Mandelic Acid.

By M. B. WATSON and G. W. YOUNGSON.

[Reprint Order No. 5132.]

(−)-Aminophenylacetic acid (α-phenylglycine) has been converted by a series of reactions into (−)-1-phenyl-1-toluene-*p*-sulphonamidoethane, which was also obtained by the action of toluene-*p*-sulphonyl chloride on (−)-1-phenylethylamine. The (−)-amino-acid is thus configurationally related to (−)-1-phenylethylamine and must belong to the D_s-series of amino-acids.

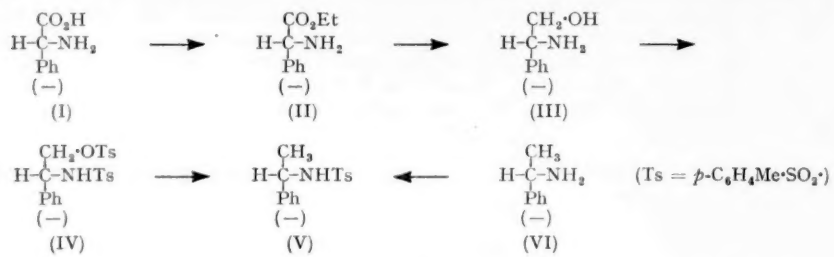
Identity of the D_s- and D_g-standards being accepted, it follows that the deamination of (−)-aminophenylacetic acid, with nitrous acid, to give L(+)-mandelic acid, is accompanied by inversion.

(−)-AMINOPHENYLACETIC ACID (α-phenylglycine) was originally assigned to the D_s-configurational series by methods based on optical comparisons (Lutz, *Ber.*, 1932, **65**, 1609; Reihlen and Knöpfle, *Annalen*, 1936, **523**, 199; and Reihlen, Knöpfle, and Sapper, *ibid.*, 1938, **534**, 247). This has been confirmed chemically, by a somewhat circuitous sequence of reactions with incompletely resolved material, by Kuna, Ovakimian, and Levene (*J. Biol. Chem.*, 1941, **137**, 337).

Optical methods applied by Clough (*J.*, 1918, **113**, 534), Freudenberg and his co-workers, and others all pointed to configurational correspondence between (−)-mandelic acid and D(−)-lactic acid. Recently this has been proved chemically by Mislow (*J. Amer. Chem. Soc.*, 1951, **73**, 3954) who completed the chain of relations between the two hydroxy-acids. (−)-Mandelic acid, therefore, belongs to the D_g-series.

The identity of the D$_S$- and the D$_g$-(and L$_S$- and L$_g$-)standards for α-amino-acids and α-hydroxy-acids is supported by the kinetic studies of Brewster, Hughes, Ingold, and Rao (*Nature*, 1950, **166**, 178) and proved from *X*-ray evidence on the structure of L-threonine (Shoemaker, Donohue, Schomaker, and Corey, *J. Amer. Chem. Soc.*, 1950, **72**, 2328) and L-hydroxyproline (Zussman, *Acta Cryst.*, 1951, **4**, 72). It follows, therefore, that (−)-aminophenylacetic acid and (−)-mandelic acid are configurationally related and that both belong to the D-series. According to the kinetic studies of Brewster, Hiron, Hughes, Ingold, and Rao (*ibid.*, p. 179), however, the two acids of *opposite* sign are configurationally related, and deamination of the (−)-amino-acid with nitrous acid to give (+)-mandelic acid takes place with *retention* of configuration. As the relative configurations of the two acids have an important bearing on the stereochemical mechanism of pinacolic deaminations and dehydrations, we thought it desirable again to investigate, by chemical methods, the configurations of both acids. The work of Mislow (*loc. cit.*), however, anticipated our study of mandelic acid, so our investigation of (−)-aminophenylacetic acid only is reported.

We have converted (−)-aminophenylacetic acid into an amine of known configuration by a two-stage reduction using lithium aluminium hydride (see Karrer *et al.*, *Helv. Chim. Acta*, 1948, **31**, 1617; 1951, **34**, 2202; 1953, **36**, 122, for similar reductions in the aliphatic series). The conversions and the steric relations are shown in the annexed scheme.



Reduction of the (−)-ester (II) in ether with lithium aluminium hydride gave the (−)-amino-alcohol (III), $[\alpha]_D^{19}$ −25·5°. The (−)-sulphonic ester (IV), which is insoluble in ether, was reduced with lithium aluminium hydride in tetrahydrofuran, to give a quantitative yield of the (−)-toluene-*p*-sulphonamide (V), $[\alpha]_D^{19}$ −78·8°. The same compound was obtained by treating the pure (−)-amine (VI), $[\alpha]_D$ −40·1°, with toluene-*p*-sulphonyl chloride, then having $[\alpha]_D^{20}$ −79·3°. Hence (−)-aminophenylacetic acid (I) is configurationally related to (−)-1-phenylethylamine (VI) and the conversion of (I) into (V) was effected without significant racemisation.

Leithe (*Ber.*, 1931, **64**, 2827) has shown that (−)-1-phenylethylamine is configurationally related to L-alanine as (VII) and (VIII). Therefore, (−)-aminophenylacetic acid and

D-alanine are related as (IX) and (X). (−)-Aminophenylacetic acid and (−)-mandelic acid are, therefore, configurationally related, and deamination of the (−)-amino-acid to (+)-mandelic acid must lead to overall inversion of configuration.

Brewster, Hiron, Hughes, Ingold, and Rao (*loc. cit.*) state that deamination by the S_N1 mechanism proceeds with racemisation and " possibly with some excess of inversion, unless a configuration-holding group, such as the α-carboxylate ion group, is present, when configuration is retained." It is difficult to see how this rule applies to aminophenylacetic acid, for it has been shown by McKenzie and Clough (*J.*, 1909, **777**) and by McKenzie and Wills (*J.*, 1925, 291) that the action of nitrous acid on (+)-aminophenylacetic acid and on its configurationally related (+)-ester follows the same steric course.

Experimental

2-Amino-2-phenylethanol.—Aminophenylacetic acid (Ingersoll and Adams, *J. Amer. Chem. Soc.*, 1922, **44**, 2933) was esterified (McKenzie and Wills, *loc. cit.*), and the ester (16 g.) in dry ether (250 c.c.) was added slowly to lithium aluminium hydride (9·7 g.) in dry ether (200 c.c.). The mixture was then refluxed on the water-bath for 3 hr. The excess of hydride was decomposed by adding water until the precipitated aluminium hydroxide coagulated in the water layer. The ether layer and extracts were dried ($MgSO_4$) and evaporated. The residual oil, which distilled at 144—147°/14 mm., solidified and had m. p. 47—49°. The amino-alcohol gave a hydrochloride, m. p. 139—140° (cf. Gabriel and Colman, *Ber.*, 1914, **47**, 1867, who give m. p. 137—138°) (Found: C, 70·0; H, 7·9. Calc. for $C_8H_{11}ON$: C, 70·1; H, 8·0%).

*2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate.*—2-Amino-2-phenylethanol (5 g.) in pyridine (15 c.c.) was added to toluene-*p*-sulphonyl chloride (13·5 g.) in pyridine (25 c.c.), and the mixture heated on the water-bath for 30 min. and then left overnight at room temperature. The pyridine was removed under reduced pressure. The residual oil solidified. Treatment with Norit and recrystallisation from aqueous alcohol gave the *toluene-*p*-sulphonamido*-ester as colourless needles, m. p. 143—144° (12·5 g., 77%) (Found: C, 59·1; H, 5·2; N, 3·2. $C_{22}H_{23}O_5NS_2$ requires C, 59·3; H, 5·2; N, 3·1%).

*Reduction of 2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate with Lithium Aluminium Hydride.*—The toluene-*p*-sulphonate (10 g.) in dry tetrahydrofuran (50 c.c.) was added gradually with stirring to lithium aluminium hydride (4·5 g.) in tetrahydrofuran (200 c.c.) The mixture was refluxed on the water-bath for 1 hr. Most of the solvent was distilled off, dry ether added, and the excess of hydride decomposed with water. The ether layer was dried ($MgSO_4$) and distilled. The residual oil, which solidified, was purified by precipitation from benzene with light petroleum (b. p. 60—80°). *1-Phenyl-1-toluene-*p*-sulphonamidoethane* crystallised from aqueous ethanol as colourless needles, m. p. 81—82° alone or mixed with the specimen described below (Found: C, 65·3; H, 6·0; N, 5·0; S, 11·7. $C_{15}H_{17}O_2NS$ requires C, 65·45; H, 6·2; N, 5·1; S, 11·6%).

*1-Phenyl-1-toluene-*p*-sulphonamidoethane.*—Toluene-*p*-sulphonyl chloride in pyridine was added to a slight excess of 1-phenylethylamine in pyridine. The mixture was kept at room temperature for 3 hr., then evaporated under reduced pressure, and an ether solution of the residue was washed several times with dilute hydrochloric acid. The compound was isolated in the usual way as needles, m. p. 81—82°, from aqueous ethanol.

*(−)-1-Phenyl-1-toluene-*p*-sulphonamidoethane.*—This *compound*, prepared as described above from (−)-1-phenylethylamine (*Org. Synth.*, 1937, **17**, 76), formed needles (from benzene–light petroleum or aqueous ethanol), m. p. 98—99°, $[\alpha]_D^{20}$ −79·3° (*c*, 2·004; *l*, 2; in C_6H_6) (Found: C, 65·3; H, 6·0; N, 5·0; S, 11·6%). The (+)-isomer, prepared in the same way from the (+)-amine, had m. p. 98—99°, $[\alpha]_D^{21}$ +79·6° (*c*, 2·003; *l*, 2; in C_6H_6).

(−)-2-Amino-2-phenylethanol.—(−)-Aminophenylacetic acid (Ingersoll and Adams, *loc. cit.*) was esterfied and the (−)-ester (15 g.) reduced in ether with lithium aluminium hydride (9 g.) as described for the racemic compound. The resulting *(−)-2-amino-2-phenylethanol* (8·25 g., 55%), however, was not distilled but, crystallised from benzene, had m. p. 75—76°, $[\alpha]_D^{19}$ −25·5° (*c*, 9·00; *l*, 2; in MeOH) [cf. Kuna, Ovakimian, and Levene, *loc. cit.*, who give $[\alpha]_D^{25}$ −15·0° (*c*, 9·06; *l*, 2; in MeOH)] (Found: C, 70·2; H, 7·9%). The (−)-amino-alcohol forms a hydrochloride, m. p. 168—169° (from ethanol–ether), $[\alpha]_D^{19}$ −25·5°, $[M]_D^{19}$ −44·3° (*c*, 2·00; *l*, 1) (cf. Reihlen, Knöpfle, and Sapper, *loc. cit.*, who resolved the racemic amino-alcohol with tartaric acid and obtained $[M]_D$ −39° to −40°).

*(−)-2-Phenyl-2-toluene-*p*-sulphonamidoethyl Toluene-*p*-sulphonate.*—The (−)-amino-alcohol (5 g.) was treated with toluene-*p*-sulphonyl chloride (13·5 g.) as already described. The resulting *compound* (12 g., 74%) crystallised from ethanol as needles, m. p. 171—172°, $[\alpha]_D^{19}$ −56·3 (*c*, 2·00; *l*, 2; in acetone) (Found: C, 59·2; H, 5·3; N, 3·1%).

This (−)-toluene-*p*-sulphonate (5 g.) was reduced in tetrahydrofuran as described for the racemic compound, to (−)-1-phenyl-1-toluene-*p*-sulphonamidoethane (2·6 g., 84%), needles (from aqueous ethanol), m. p. and mixed m. p. 98—99°, $[\alpha]_D^{19}$ −78·8° (*c*, 2·00; *l*, 2; in C_6H_6) (Found: C, 65·4; H, 6·1; N, 4·9; S, 11·3%).

Robert Gordon's Technical College, Aberdeen. [*Received, February 17th*, 1954.]

The Formation of Ketones. Part II. The Formation of Some Substituted* cyclo*Pentanones by the Dieckmann Reaction.*

By R. I. Reed and (Miss) M. B. Thornley.

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Ring closure of some alkyl-substituted esters by sodium ethoxide is in accord with the accepted course of the reaction, the rate-determining steps being ring closure and ring fission in the forward and reverse reactions respectively. Some evidence has been obtained for the existence of steric retardation.

Although many investigations have been made into the formation of β-keto-esters (Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons Ltd., London, 1953, p. 787), no kinetic studies have been reported, and, for comparison with the pyrogenic formation of ketones, some studies of the Dieckmann reaction (*Ber.*, 1849, **27**, 102; *Annalen*, 1901, **317**, 51) have been undertaken.

Initially the investigation has been confined to the cyclisation of some adipic esters, the overall reaction being

$$EtO_2C\cdot[CH_2]_2\cdot CHR'\cdot CHR\cdot CO_2Et \overset{NaOEt}{\rightleftharpoons} EtO_2C\cdot CH(OC)\cdot CH_2\cdot CHR'\cdot CHR + EtOH$$

where R = H, Me, Et, Pr^i, and R′ = H, or R = H and R′ = Me. Evidence for the direction of ring closure has been provided for the α-methyl- (Dieckmann, *Annalen*, 1901, **317**, 51; Cornubert and Borrel, *Bull. Soc. chim.*, 1930, **47**, 301) and β-methyl-adipic ester (Dieckmann and Groenveld, *Ber.*, 1900, **33**, 595; Chakravarti, *J.*, 1947, 1028; Craig, unpublished work). In the other cases, a single product was obtained whose configuration was deduced by analogy. Use of a large excess of sodium ethoxide leads to a first-order reaction, and a formal demonstration of this for diethyl adipate is reported in Table 1.

Table 1.—Temp. 40·0°. (2·85 ± 0·05)M-NaOEt.

Ester, mole :	0·089	0·110	0·198	0·220
10^3k (min.$^{-1}$) [a]	4·34	4·23	4·31	4·37
10^3k_1 (min.$^{-1}$) [a]	[b]	3·21	3·43	3·48
10^3k_{-1} (min.$^{-1}$)	—	1·02	0·88	0·89

[a] k represents the overall velocity constant, k_1 that for ring closure, and k_{-1} that for the ring-opening reaction. [b] Equilibrium value rather too small for an accurate determination of k_1.

Table 2. (2·85 ± 0·05)M-NaOEt.[a]

Substituent, R	R′	35° k_1	35° k_{-1}	40° k_1	40° k_{-1}	45° k_1	45° k_{-1}	50° k_1	50° k_{-1}	E_1 (kcal.)	E_{-1} (kcal.)	A_1 (min.$^{-1}$)	A_{-1} (min.$^{-1}$)
H	H	1·68	0·48	3·16	1·00	5·34	1·21	13·0	2·72	24·0	23·9	$4·9 \times 10^{13}$	$3·0 \times 10^{12}$
				3·44	0·89								
Me	H	1·61	1·01	2·36	2·15	3·83	2·46	—	—	17·5	17·7	$1·2 \times 10^{9}$	$1·1 \times 10^{9}$
Et	H	1·32	1·13	2·52	2·62	4·75[b]	3·81[b]	7·01	6·87	25·2	24·2	$3·0 \times 10^{14}$	$4·5 \times 10^{13}$
Pr^i	H	Too slow for measurement				1·26	1·11	—	—	—	—	—	—
H	Me	—	—	—	—	16·9[c]	5·22	—	—	—	—	—	—

[a] All velocity constants are $\times 10^3$ (min.$^{-1}$). [b] Values obtained by interpolation. [c] We are indebted to R. S. Craig for the preparation of, and preliminary measurements on, this compound.

The measured velocity constants for the homologous series, together with the Arrhenius factors, are in Table 2.

In accordance with the accepted mechanism (Ingold, *op. cit.*), it is convenient to consider the overall reaction as composed of stages (I—IV). Anion formation (I) is not, under

* Part I, *J.*, 1953, 3911.

the present conditions, the rate-determining step. By a consideration of known electron-displacement effects, it can be predicted that the influence of the alkyl groups on the ionisation would lead to the order H, β-Me, α-Et, α-Me, for the velocity constants, which is not in accord with observation, and, by similar argument, enolisation (IV) can also be shown

(I) $EtO_2C\cdot CH_2\cdot[CH_2]_2\cdot CHR\cdot CO_2Et + EtO^- \rightleftharpoons EtO_2C\cdot CH^-\cdot[CH_2]_2\cdot CHR\cdot CO_2Et + EtOH$

(II) $EtO_2C\cdot CH^-\cdot[CH_2]_2\cdot CHR\cdot CO_2Et \rightleftharpoons -\{O{=}C(OEt)\cdot CHR\cdot CH_2\cdot CH(CO_2Et)\cdot CH_2\}$ (*b*)

(III) $-\{O{=}C(OEt)\cdot CHR\cdot CH_2\cdot CH(CO_2Et)\cdot CH_2\} \rightleftharpoons O{=}C(CHR\cdot CH_2\cdot CH(CO_2Et)\cdot CH_2) + EtO^-$

(IV) $EtO_2C\cdot CH\cdot[CH_2]_2\cdot CHR + EtO^- \rightleftharpoons EtO_2C\cdot C\cdot[CH_2]_2\cdot CHR + EtOH$ (OC ⟷ −O·C)

not to be rate-determining. The importance of the enolisation is that in the presence of the high ethoxide concentration the amount of keto-form present will be reduced to a low equilibrium value, which in the absence of detailed information has been assumed to be of the same order of magnitude for all the cases here described.

Under the experimental conditions used—a solvent of low dielectric constant and a high concentration of sodium ethoxide—the reaction is bimolecular, which is supported by the qualitative observation that the rate of reaction increases with increasing basic strength, the order being $MeO^- < EtO^- \sim Pr^nO^- < Pr^iO^-$. The transition state (II*b*) has been considered, in view of the high stability made possible by mesomerism, as a reaction intermediate, and its formation and decomposition are here considered as two distinct processes.

In ring closure, the approach of the anionic centre will be facilitated by a positive charge on the future ketonic carbon atom, and the loss of the ethoxide ion is retarded. Thus, if the former is rate-determining, the presence of adjacent alkyl groups should progressively retard ring formation, which is in general agreement with the measured velocity constants (H > α-Me, α-Et). The overall process is, however, complicated by the polarisation which

$-\{O{=}C(OEt)\cdot CHR\cdot CH{-}\} \rightleftharpoons -O{-}C(OEt)\cdot CHR\cdot CH{-}$

will facilitate ring-closure by enolisation and either ring fission, or loss of ethoxide ion, by the return to the ketonic form, and in consequence the agreement with simple theory may not be quantitative.

The reverse process, ring opening, has the opposite electronic requirements, and hence the presence of alkyl substituents should hinder the addition of the ethoxide ion to give the complex and facilitate breakdown of the intermediate so formed. The latter is in accordance with the observations, and the order of the velocity constants (H < α-Me < α-Et) is in agreement with the known electron-release of the respective alkyl groups. In both reactions it appears that the rate-determining process is associated with the carbon–carbon bond of the intermediate and not with the concomitant loss or gain of the ethoxide ion.

Some evidence has been obtained for the existence of a steric factor caused by the increasing bulk of the α-alkyl substituent, which appears to be the probable cause of the retardation of ring opening of ethyl 2-oxo-3-*iso*propyl*cyclo*pentanecarboxylate relative to that of the lower homologues in which a progressive acceleration was observed. The possibility that all α-substituents cause some steric retardation has also been examined by a comparison of ring fissions of ethyl 2-oxo-3-ethyl*cyclo*pentanecarboxylate and the analogous 4-methyl compound, whose electronic effects may be considered equal, to a first approxim-

ation, the principal difference being the spatial atomic arrangement. The methyl derivative reacts faster by a factor of about 1·4, indicating that the effect is not large in this

direction, whilst the forward reaction may be complicated by other factors, the incursion of some of which have already been noted in the ring-closure process. This work is being continued and extended to the analogous pimelic esters.

Experimental

(2·85 ± 0·05)M-Sodium ethoxide was prepared by dissolving sodium under reflux in the calculated quantity of ethyl alcohol. Gentle heating was necessary in the final stages, and the concentration estimated by titration. The ethoxide solution slowly became brown and was freshly prepared for each set of experiments. Sufficient ester to make an approx. 0·1M-solution was weighed into a graduated flask, brought to the temperature of the thermostat, and made up to the mark with the ethoxide solution already at thermostat temperature. On mixing, the solution became very viscous and vigorous shaking for several minutes was necessary to make the solution homogeneous. Aliquot samples were withdrawn at suitable intervals and analysed for the β-keto-ester present (Cumming, Hopper, and Wheeler, " Systematic Organic Chemistry," Constable & Co. Ltd., London, 1937, p. 496), the accuracy having been tested for ethyl 2-oxo-*cyclo*pentanecarboxylate [Found : (*a*) 4·810; 4·635; (*b*) 5·705, 5·721. Prepared : (*a*) 4·786; (*b*) 5·705 g./l.].

Within individual kinetic experiments, the variation in velocity constants was small, the results of a typical experiment being given in Table 3.

Table 3.—Temp. 35·1°. 0·137M-Diethyl adipate. 2·83M-Sodium ethoxide.

Time (min.)	0	30	60	90	120	150	180
10^3k (min.$^{-1}$)	—	2·18	2·11	2·22	2·15	2·14	2·10

Materials.—" Absolute " ethyl alcohol was repeatedly dried (Mg) and distilled; it had b. p. 78·5°/760 mm. Adipic acid (from Messrs. Light & Co.) was recrystallised from water to m. p. 150°. Its diethyl ester had b. p. 130°/14 mm. β-Naphthol (from British Drug Houses Ltd.) was steam-distilled and recrystallised from ethanol, then having m. p. 123°. Bromine (from British Drug Houses Ltd.) was shaken twice with concentrated sulphuric acid and distilled, having b. p. 59°.

α-Alkyladipic acids. 3-Phenoxypropyl bromide (*Org. Synth.*, Coll. Vol. I, 1946, p. 435) was condensed with ethyl sodiomethylmalonate. Hydrolysis of the product with 30% aqueous potassium hydroxide and decarboxylation at 210° gave α-methyl-δ-phenoxyvaleric acid which was converted into the iodo-acid by constant-boiling hydriodic acid and then esterified (Vogel, " Practical Organic Chemistry," Longmans Green & Co., London, 1948, p. 380). The ester, b. p. 180°/16 mm., was converted by alcoholic potassium cyanide into the cyano-ester, which was hydrolysed to α-methyladipic acid. Recrystallisation to constant m. p. gave an acid of m. p. 63°, giving (method : *op. cit.*) a diethyl ester, b. p. 127—129°13 mm.

α-Ethyl-, m. p. 48°, and α-*iso*propyl-adipic acid, m. p. 40—42° (diethyl esters, b. p. 130°/12 mm. and 138—140°/15 mm., respectively), were similarly prepared.

One of us (M. B. T.) is indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance.

University of Glasgow. [*Received, February 22nd,* 1954.]

A Correction to " meta*-Interactions and Inductive Effects in Heterocyclic Systems."*

By D. A. Brown and M. J. S. Dewar.

[Reprint Order No. 4802a.]

Professor Herbert C. Brown has drawn our attention to several passages in our paper of the above title (*J.*, 1953, 2406) in which we attributed to him and his co-author (H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, 1951, **73**, 3308) the view that the prototropic reactivity which they had discovered for the methyl group in β-picoline is due to *m*-quinonoid structures stabilizing the conjugate carbanion. This view we criticised and rejected on the basis of molecular-orbital calculations.

Professor Brown points out that, in actual fact, he and his co-author clearly and explicitly stated in their paper that stabilization by *m*-quinonoid structures could *not* be the explanation and that an alternative one must be sought.

We entirely agree with this statement of the facts. We greatly regret that, through inadvertence, we so completely misrepresented their views.

Queen Mary College, London, E.1. [*Received, November 17th*, 1953.]

The Chemistry of Ribose and its Derivatives. Part III. The Separation of Anomeric Methyl Ribosides.*

By G. R. Barker and D. C. C. Smith.

[Reprint Order No. 5107.]

Synthesis of derivatives of ribose from methyl ribosides would be greatly facilitated if single anomeric forms of these compounds were readily available. Minsaas (*Annalen*, 1934, **512**, 286) obtained methyl β-D-ribopyranoside by a lengthy process of crystallisation of the mixture of anomers, and Jeanloz, Fletcher, and Hudson (*J. Amer. Chem. Soc.*, 1948, **70**, 4055) obtained it from **2 : 3 : 4**-tri-*O*-benzoyl-β-D-ribopyranosyl bromide. The corresponding α-isomer has not been described and the methyl ribofuranosides (Barker, *J.*, 1948, 2035) were obtained only as a mixture of anomeric forms. We therefore attempted to isolate all four isomers by the method of Hough, Jones, and Wadman (*J.*, 1950, 1702) which has been used successfully also by Augestad, Berner, and Weigner (*Chem. and Ind.*, 1953, 376).

Mixtures of the methyl α- and β-ribosides were separately placed on columns of powdered cellulose, and elution from the columns was followed polarimetrically. In each case early fractions showed an increasing negative rotation and yielded the β-isomer. Thereafter, a mixture of α- and β-isomers was obtained, and was resolved by repeated chromatography. Methyl β-ribopyranoside crystallised immediately and had almost the same physical properties as those reocrded by Minsaas (*loc. cit.*); the other three isomers have not crystallised after three years, but it is probable that in each case complete separation of α- and β-forms had been achieved since each was chromatographically homogeneous. The identities of the isomers were confirmed by the fact that each consumed the expected quantity of sodium metaperiodate and the rotations of the solutions after completion of the oxidation corresponded to the specific rotations of the expected dialdehydes previously recorded (Jackson and Hudson, *J. Amer. Chem. Soc.*, 1937, **59**, 994). From the specific rotations of the four glycosides it was calculated that the original mixtures of furanoside and pyranoside anomers contained 68 and 74%, respectively, of the β-forms.

If the molecular rotations of these anomeric pairs were known the ring structure of crystalline ribose itself might be indicated. Phelps, Isbell, and Pigman (*ibid.*, 1934, **56**,

* Part II, *J.*, 1950, 23.

747) considered that the crystalline sugar is probably β-D-ribofuranose on account of the initial direction of the mutarotation and of its similarity in behaviour to the mannose–calcium chloride compound which also exhibits complex mutarotation (Dale, *ibid.*, 1929, **51**, 2225) and gives a γ-lactone on oxidation with bromine (Isbell, *ibid.*, 1933, **55**, 2166). Unfortunately, crystalline D-ribose is known in only one form, and hence calculation of the partial molecular rotation of carbon atoms 2—5 has not so far been possible. However, by application of the rules of isorotation the molecular rotation of the anomer of crystalline D-ribose can be predicted approximately from the molecular rotations of the four methyl D-ribosides. Thus the algebraic sums of the molecular rotations * of the methyl α- and β-D-ribofuranosides and of the methyl α- and β-D-ribopyranosides are respectively +139° and −5°; these figures represent the relative partial rotation due to carbon atoms 2—5. It being assumed that the partial molecular rotation of this part of the molecule is the same in the free sugar, and the molecular rotation of crystalline D-ribose being taken as −36° †, then the molecular rotation of its anomer would be approximately +175° if furanose, or +31° if pyranose. According to the rules of isorotation the algebraic difference between the molecular rotations of the α- and the β-form of any sugar derivative is a measure of the partial molecular rotation of $C_{(1)}$, and hence depends largely on the nature of the substituent at this position. In accordance with this, the difference between the molecular rotations of the methyl D-ribopyranosides (+345°) agrees well with the published differences for the other methyl pentopyranosides (D-xylose, +360°; D-lyxose, +308°; L-arabinose, +375°; cf. Bates, " Polarimetry, Saccharimetry, and the Sugars," National Bureau of Standards, 1942, p. 708 *et seq.*). The methyl D-ribofuranosides show a similar difference (+343°) which suggests that $C_{(1)}$ has the same partial molecular rotation in both furanoside and pyranoside structures. In the free sugars, the ribofuranoses or ribopyranoses might be expected to show molecular-rotation differences between α- and β-forms similar to those observed for other sugars (galactose, +176°; glucose, +168°; lactose, +187°; mannoheptose, +177°; cf. Bates, *loc. cit.*). The difference between the molecular rotations of α- and β-ribose, derived from the observed rotation of crystalline D-ribose and the predicted rotation of its anomer would be +211° if furanose and +77° if pyranose. These figures suggest that crystalline D-ribose has the furanose configuration. However, there are sugars whose molecular-rotation differences do not fall into line with those quoted (lyxose, +117°; mannose, +83°; talose, +99°), and since ribose behaves anomalously in other ways, it is impossible to draw a firm conclusion. The properties of the four methyl ribosides are, however, recorded below in order that a decision may be reached when further data become available.

	Methyl D-ribofuranoside		Methyl D-ribopyranoside	
	α-form	β-form	α-form	β-form
$[\alpha]_D^{20}$ (*c*, 1·0 in MeOH)	+146·8°	−62·4°	+103·3°	−106·5°
Molecular rotation, [*M*]	+241	−102	+170	−175
$[M]_\alpha - [M]_\beta$	+343		+345	
$[M]_\alpha + [M]_\beta$	+139		−5	
Mols. $NaIO_4$ reduced [1]	0·99	0·94, 1·06	1·9	1·97
[α] of oxidation product	+116·3°	−145·3°	+122°	−125·5°
[α] of expected dialdehyde [2]	+117·3 to +121·1	−148·1 to −150·6	+124·2 to +125·2	−123·7 to −124·3

[1] By Barneby's method (*J. Amer. Chem. Soc.*, 1916, **38**, 330). [2] Jackson and Hudson, *loc. cit.*

Experimental.—Methyl α- and β-ribofuranosides. The mixed glycosides were obtained by Barker's method (*loc. cit.*). Paper chromatography with *n*-butanol–water as the solvent system gave two spots of R_F values 0·32 and 0·45. The syrupy mixture (5·4 g.) in *n*-butanol (30 c.c.) was saturated with water and loaded on to a column of " Solkafloc " prepared by Campbell, Mellangy, and Work's method (*Biochem. J.*, 1951, **48**, 109) and eluted with *n*-butanol saturated with water, 6-c.c. fractions being collected. Fractions having a progressively increasing negative rotation were combined and yielded, after removal of the solvent, chromatographically homogeneouss yrupy methyl β-D-ribofuranoside (0·89 g.; R_F, 0·45) which was sublimed at 0·01 mm.

* For convenience, molecular rotations [*M*] as quoted in this paper are defined as [α] × mol. wt./100.
† Extrapolation of the mutarotation curve given by Phelps *et al.* (*loc. cit.*) to zero time gives a specific rotation of −24·0° for crystalline D-ribose.

(Found: OMe, 19·7. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Fractions having a progressively decreasing negative rotation were discarded. Fractions having a positive rotation were combined and after removal of the solvent a syrup was obtained which was not chromatographically homogeneous. The material was rechromatographed by the same method, the fractions being examined by paper chromatography. Those containing only the component of R_F 0·32 were combined, the solvent was removed as before, and the remaining syrupy methyl α-D-ribofuranoside (0·23 g.) was sublimed at 0·01 mm. (Found: OMe, 19·5. Calc. or $C_6H_{12}O_5$: OMe, 18·9%).

Methyl α- and β-ribopyranosides. The mixed glycosides were prepared by Minsaas's method (*loc. cit.*). Paper chromatography in the *n*-butanol–water system gave two spots of R_F values 0·32 and 0·45. The mixture (6 g.) was dissolved in the upper layer of a mixture of pyridine, ethyl acetate, and water (1 : 2 : 2), and loaded on to a column as described above and eluted with the same mixture of solvents. Eluates were examined polarimetrically as before and from the early fractions chromatographically homogeneous syrupy methyl β-D-ribopyranoside (0·95 g.; R_F, 0·45) was obtained. After being sublimed at 0·01 mm. the compound crystallised within 1 hr. and had m. p. 78° (Found: OMe, 18·0. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). Later fractions, after being re-chromatographed twice, gave chromatographically homogeneous syrupy methyl α-D-ribopyranoside (0·065 g.; R_F, 0·32), and was sublimed at 0·01 mm. (Found: OMe, 18·5. Calc. for $C_6H_{12}O_5$: OMe, 18·9%).

One of us (D. C. C. S.) gratefully acknowledges the receipt of a maintenance grant from the Department of Scientific and Industrial Research.

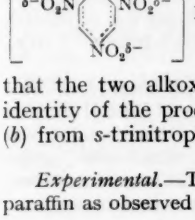
THE UNIVERSITY, MANCHESTER. [*Received, February 10th*, 1954.]

Potassium Ethyl 1-Methoxypicrate.

By R. FOSTER and D. LL. HAMMICK.

[Reprint Order No. 5109.]

WE have measured the infra-red absorption of the product of interaction of *s*-trinitroanisole with potassium ethoxide. The spectrum shows several interesting features. The N–O symmetrical stretching frequencies appear to have shifted from 1343 cm.$^{-1}$ in *s*-trinitroanisole to 1291 cm.$^{-1}$ in the product. Similarly the N–O asymmetrical stretching frequencies have shifted from 1552 to 1492 cm.$^{-1}$. These bands have been assigned by Randle and Whiffen (*J.*, 1952, 4153) the values 1349 ± 9 and 1518 ± 13 cm.$^{-1}$ respectively. Another feature of the spectrum is that the Ar–H stretching frequency at 3090—3000 cm.$^{-1}$ is absent. It is suggested that these differences are due to an increased negative charge on the nitro-groups, supporting the annexed structure (Sidgwick, "Organic Chemistry of Nitrogen," ed. Taylor and Baker, Oxford Univ. Press, 1937, p. 260).



Confirmation of the conclusions of Meisenheimer (*Annalen*, 1902, **323**, 219) and of Jackson and Earle (*Amer. Chem. J.*, 1903, **29**, 89) that the two alkoxy-groups are symmetrically disposed in the molecule is given by the identity of the products obtained (*a*) from *s*-trinitroanisole and potassium ethoxide and (*b*) from *s*-trinitrophenetole and potassium methoxide (Meisenheimer, *loc. cit.*).

Experimental.—The spectra measured were those of solid films dispersed as mulls in liquid paraffin as observed with a Perkin–Elmer double-beam spectrometer with a rock-salt prism.

We thank Dr. F. B. Strauss for helpful discussions, and the Department of Scientific and Industrial Research for a maintainance grant to one of us (R. F.).

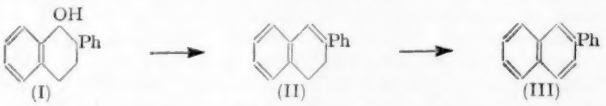
DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 10th*, 1954.]

Synthesis of 2-Phenylnaphthalene.

By Neil Campbell and David Kidd.

[Reprint Order No. 5096.]

Only a few convenient syntheses of 2-phenylnaphthalene are known (Spring, *J.*, 1934, 1332; Hey and Wilkinson, *J.*, 1940, 1030; Weizmann, Bergmann, and Bograchov, *Chem. and Ind.*, 1940, **59**, 402; Price and Ciskowski, *J. Amer. Chem. Soc.*, 1938, **60**, 2502). We now report an easy method starting from readily accessible substances. Benzyl cyanide and phenethyl bromide afford a product which is hydrolysed to αγ-diphenyl-



(I) (II) (III)

butyric acid. Ring-closure of the acid gives 2-phenyl-1-tetralone, which is reduced quantitatively by lithium aluminium hydride to 2-phenyl-1-tetralol (I). The tetralol is converted into 2-phenylnaphthalene (III) either by treatment with thionyl chloride or by dehydration to 3 : 4-dihydro-2-phenylnaphthalene (II) and subsequent dehydrogenation with chloranil. In the first process dehydration must be accompanied by chlorination followed by dehydrochlorination.

The yields at all stages except the first (62%) are 90% or more.

Experimental.—*2-Phenyl-1-tetralol.* Freshly distilled benzyl cyanide (82·5 g.) was added during ½ hr. to " molecular " sodium (16·2 g.) covered by dry ether (300 ml.). The mixture was stirred and boiled for 2 hr. and cooled in ice-water, and to it was added with brisk stirring phenethyl bromide (60 g.) during 2 hr. Stirring was continued overnight, and the ether boiled off and replaced by a similar volume of dry benzene. The mixture was boiled for 3 hr., and hydrolysed with dilute hydrochloric acid. The organic layer was separated, washed with water, dried, and evaporated to give α-diphenylbutyronitrile (44 g.), b. p. 152—156°/1 mm. The nitrile was hydrolysed with 70% sulphuric acid and acetic acid for 2 days : the resulting αγ-diphenylbutyric acid (94%), crystallised twice from light petroleum (b. p. 60—80°), had m. p. 72—73° (lit., 70—72°).

The acid was converted into the acid chloride which underwent ring-closure by the inverse Friedel–Crafts reaction (Johnson and Glenn, *J. Amer. Chem. Soc.*, 1949, **71**, 1094), giving 2-phenyl-1-tetralone (almost quantitative yield), m. p. 75·5—76·5° after crystallisation from ethanol (lit., 76—77°). The tetralone (7·40 g., 0·033 mol.) in dry ether (100 ml.) was added to a solution of lithium aluminium hydride (1 g., 0·025 mol.) in dry ether (200 ml.) during 30 min. The solution was boiled (3 hr.) and the excess of hydride was decomposed by addition of water and then dilute sulphuric acid to the cooled solution. The organic layer was separated, washed with water, and dried (Na_2SO_4). Removal of the ether gives 2-phenyl-1-tetralol (7·10 g., 95%), needles (from light petroleum, b. p. 60—80°), m. p. 67—68°.

2-Phenylnaphthalene. (*a*) The tetralol (3·90 g.) reacted vigorously with thionyl chloride (12 ml.), and the solution after 1 hr. was boiled for the same period. Excess of thionyl chloride was removed *in vacuo* and finally by co-distillation with dry benzene. The residue was crystallised from methanol, giving 2-phenylnaphthalene (3·18 g., 90%), which was further purified by passing its solution in benzene–light petroleum (1 : 3) down a short alumina column. A yellow impurity remained on the column and pure 2-phenylnaphthalene was obtained from the filtrate.

(*b*) The tetralol (2·00 g., 0·009 mole) was shaken (5 hr.) with phosphoric oxide (2·56 g., 0·018 mole) in dry benzene (50 ml.). Water and then ether were added and the ether layer was washed successively with 5% sodium carbonate solution and water. The dried solution was evaporated and the residual 3 : 4-*dihydro-2-phenylnaphthalene* (1·84 g.) crystallised from methanol in colourless blades, m. p. 64—66° (Found : C, 93·1; H, 6·9. $C_{16}H_{14}$ requires C, 93·1; H, 6·9%). The *trinitrobenzene* derivative formed golden-yellow blades (from ethanol), m. p. 110—111° (Found : N, 13·5. $C_{28}H_{20}O_{12}N_6$ requires N, 13·3%). The dihydro-compound (1·03 g., 0·005 mole) and chloranil (1·27 g., 0·005 mole) were boiled (15 hr.) in sulphur-free xylene.

Ether was added and the solution shaken with successive portions of 4% aqueous potassium hydroxide until the alkaline washings were colourless. The organic layer was washed with water and dried (Na_2SO_4), and the solvents were removed by distillation *in vacuo*. The residue in benzene–light petroleum (b. p. 60—80°) (1 : 2) was passed down a short alumina column. Elution of a pale blue fluorescent band gave 2-phenylnaphthalene (90%), m. p. 101—102° (lit., 101—102°), identified by its m. p. and those of the trinitrobenzene derivative, m. p. 112—113·5° (lit., 113·5—115·5°), and the trinitrofluorenone derivative, m. p. 170—171° (lit., 169·5—170·5°).

Thanks are expressed to the D.S.I.R. for a maintenance grant (to D. K.) and to the Anglo-Iranian Oil Co. Ltd. for a grant.

UNIVERSITY OF EDINBURGH. [*Received, February 8th*, 1954.]

Branched-chain Sugars. Part II. The Action of Grignard Reagents on* 1 : 2-3 : 4-*Di*-O-iso*propylidene*-6-O-*toluene*-p-*sulphonyl*-α-D-*galactose.*

By W. G. OVEREND and G. VAUGHAN.

[Reprint Order No. 5094.]

GILMAN and his co-workers (Gilman and Beaber, *J. Amer. Chem. Soc.*, 1923, **45**, 839; Gilman and Heck, *ibid.*, 1928, **50**, 2223) concluded that reaction of organomagnesium halides with aryl esters of sulphonic acids gives sulphones and phenols, whereas with alkyl sulphonates alkylation occurs together with the formation of some alkyl halide, in accordance with the equations :

$$ArO{\cdot}SO_2{\cdot}R + R'{\cdot}MgX \longrightarrow ArO{\cdot}MgX + R'{\cdot}SO_2{\cdot}R \quad (1)$$

$$AlkO{\cdot}SO_2{\cdot}R + R'{\cdot}MgX \longrightarrow Alkyl{\cdot}R' + R{\cdot}SO_2{\cdot}O{\cdot}MgX \quad (2)$$

$$AlkO{\cdot}SO_2{\cdot}R + R{\cdot}SO_2{\cdot}O{\cdot}MgX \longrightarrow Alkyl{\cdot}X + (R{\cdot}SO_2{\cdot}O)_2Mg \quad (3)$$

(X = halide, R′ = alkyl.)

If toluene-*p*-sulphonyl esters of carbohydrates could be induced to react with alkylmagnesium halides according to reactions 2 and 3, the products would be of interest from several viewpoints. Reaction 2 would yield a *C*-alkyl sugar, and it was hoped to realise an independent synthesis of the *C*-alkyl sugars formed by the action of Grignard reagents on methyl 2 : 3-anhydrohexosides (Newth, Richards, and Wiggins, *J.*, 1950, 2356; Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308). Reaction 3 would produce halogenated sugars which are useful intermediates in the synthesis of deoxy-sugars (see Overend, Stacey, *et al.*, *J.*, 1949, 1235, and later papers). However, 1 : 2-3 : 4-di-*O-iso*propylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose and methylmagnesium iodide in ether gave 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose as sole isolatable product. A similar result was obtained with ethylmagnesium iodide. Attempts to demonstrate the presence, respectively, of ethyl- and propyl-pentose derivatives were unsuccessful. The identity of each product was confirmed by its smooth reduction to 6-deoxy-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose (di-*O-iso*propylidene-D-fucose). Variation of the proportions of the Grignard reagent and the toluene-*p*-sulphonyl derivative of di-*O-iso*propylidene-galactose had no effect on the nature of the product and little effect on the yield. No reaction occurred between phenylmagnesium iodide and this D-galactose derivative, or with methylmagnesium iodide and toluene-*p*-sulphonyl esters formed from secondary hydroxyl groups : 1 : 2-5 : 6-di-*O-iso*propylidene-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose and methyl 2-*O*-toluene-*p*-sulphonyl-β-L-arabinoside and its diacetate were recovered almost quantitatively. In view of the yields of 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose obtained in our experiments it is probably formed by the reaction scheme originally proposed by Kenyon *et al.* (Kenyon, Phillips, and Turley, *J.*, 1925, 399;

* Part I, *J.*, 1953, 3308.

Holmberg, *Ber.*, 1926, **59**, 1558; see also Rossander and Marvel, *J. Amer. Chem. Soc.*, 1928, **50**, 1491) rather than according to reactions 2 and 3 above.

Experimental.—Reaction of 1 : 2-3 : 4-*di*-O-iso*propylidene*-6-O-*toluene*-p-*sulphonyl*-α-D-*galactose with alkylmagnesium iodides.* (*a*) With methylmagnesium iodide. To methylmagnesium iodide prepared from magnesium (0·243 g.) and methyl iodide (1·46 g.) in ether was added an ethereal solution of 1 : 2-3 : 4-di-*O-iso*propylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose (4·14 g.). The mixture was heated under reflux for 5 hr. and then kept at room temperature overnight. After dilution with ether and water, 2N-hydrochloric acid was added until the precipitate had redissolved. The ethereal layer was separated, washed successively with water, saturated sodium hydrogen carbonate solution, dilute sodium thiosulphate solution, and water, and then dried (Na_2SO_4). Evaporation of the solvent yielded an oil which distilled as a colourless syrup, b. p. 140—145° (bath-temp.)/0·003 mm., which crystallised on trituration. Recrystallisation from ethanol gave 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose (2·5 g.), m. p. 70° alone or on admixture with an authentic specimen, $[\alpha]_D^{14}$ −50·2° (*c*, 1·59 in $CHCl_3$) (Found : C, 38·8; H, 4·8. Calc. for $C_{12}H_{19}O_5I$: C, 38·9; H, 5·1%).

Reductive dehalogenation gave quantitatively 6-deoxy-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose, m. p. 37—38°, $[\alpha]_D^{13}$ −52·9° (*c*, 2·04 in $CHCl_3$) (Found : C, 59·1; H, 8·2. Calc. for $C_{12}H_{20}O_5$: C, 59·0; H, 8·2%), and removal of the *iso*propylidene group gave 6-deoxy-6-iodo-D-galactose, m. p. 110° alone or on admixture with an authentic specimen prepared according to Raymond and Schroeder (*J. Amer. Chem. Soc.*, 1948, **70**, 2785).

(*b*) With ethylmagnesium iodide. The reaction was carried out in a similar manner with ethylmagnesium iodide [prepared from magnesium (0·243 g.) and ethyl iodide (0·83 c.c.) in ether] and 1 : 2-3 : 4-di-*O-iso*propylidene-6-*O*-toluene-*p*-sulphonyl-α-D-galactose (4·14 g.), and again 6-deoxy-6-iodo-1 : 2-3 : 4-di-*O-iso*propylidene-α-D-galactose (2·4 g.), m. p. 70°, was isolated.

The authors thank Professor M. Stacey, F.R.S., for his interest and Dr. R. Allerton for providing some of the initial materials. One of them (G. V.) thanks the Dunlop Rubber Co. Ltd. for financial support.

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The Heats of Formation of Phosphorus Trichloride, Sulphuryl Chloride, and Thionyl Chloride.

By E. NEALE and L. T. D. WILLIAMS.

[Reprint Order No. 5022.]

WE recently reported (*J.*, 1952, 4535) heats of hydrolysis of phosphorus trichloride and oxychloride significantly larger than those due to Thomsen (" Thermochemische Untersuchungen," 1882, Vol. 2), and our results were substantially confirmed by Charnley and Skinner (*J.*, 1953, 450). In computing heats of formation from the experimental results, data given in " Selected Values of Chemical Thermodynamic Properties " (National Bureau of Standards, Circular 500) were used for the heats of formation of the hydrolysis products. Charnley and Skinner in commenting on the reliability of the latter pointed out that while the value for phosphoric acid is based on two independent measurements which are in good agreement, that for phosphorous acid depends solely on the work of Thomsen (*op. cit.*). In view of this it was decided to repeat measurements on phosphorus trichloride, carrying out the hydrolysis in bromine water and thus producing phosphoric acid directly and avoiding reference to phosphorous acid.

This work was preliminary to an investigation of the thermochemistry of organic phosphorus compounds (to be reported shortly). As certain oxidation reactions in this programme required the use of sulphuryl chloride, it was also necessary to check its heat of hydrolysis and that of its reduction product—thionyl chloride—since here aga in

published data are based on unconfirmed work by Thomsen (*op. cit.*) for the former and by Ogier (*Compt. rend.*, 1882, **94**, 82) for the latter chloride.

Experimental.—Purification of compounds. Phosphorus trichloride and sulphuryl chloride were fractionally distilled through a Dufton column (PCl_3 in an atmosphere of nitrogen). Thionyl chloride was distilled first over quinoline and finally over linseed oil.

Calorimeter. This was that used in the earlier work (*loc. cit.*); calibration was done electrically. The samples were contained in glass ampoules which were broken under the surface of the liquid. The calorimeter liquid was 500 ml. of distilled water in all cases, with the addition of 7—8 g. of bromine in the case of phosphorus trichloride and a little powdered iodine in that of sulphuryl chloride.

All measurements were carried out between 22° and 23°.

In the experiments with phosphorus trichloride the products were analysed for phosphoric acid (by Wilson's quinoline phosphomolybdate method, *Analyst*, 1951, **76**, 65) after removal of the excess of bromine with sodium sulphite. The hydrolysis products from both sulphuryl and thionyl chloride were analysed for chloride.

The observed heats ($\Delta H_{obs.}$) in the Tables refer to the reactions:

$$PCl_3(l.) + Br_2(aq.) + 4H_2O(l.) \longrightarrow H_3PO_4(aq.) + 3HCl(aq.) + 2HBr(aq.)$$
$$SO_2Cl_2(l.) + 2H_2O(l.) \longrightarrow H_2SO_4\ (aq.) + 2HCl(aq.)$$
$$SOCl_2(l.) + 2H_2O(l.) \longrightarrow H_2SO_3(aq.) + 2HCl(aq.)$$

The subsidiary thermochemical data used in deriving heats of formation ($\Delta Hf°$) were taken from National Bureau of Standards, Circular 500. The results are summarised in the Table.

(a) *Reaction of phosphorus trichloride with bromine water.*

Wt. (g.)	Moles of H_2O per mole of PCl_3	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ PCl_3(l.) (kcal.)	Wt (g.)	Moles of H_2O per mole of PCl_3	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ PCl_3(l.) (kcal.)
1·0749	3500	−137·8	−74·5	0·5848	6300	−137·5	−74·8
0·6741	5500	−138·6	−73·7	0·6573	5600	−138·1	−74·2
0·6819	5400	−137·3	−75·0	0·7810	4700	−138·4	−73·9
					Mean values	−137·9	−74·4

Recovery of H_3PO_4 in the reaction products varied from 100·0 to 100·9%.

(b) *Hydrolysis of sulphuryl chloride with iodine as catalyst.*

Wt. (g.)	Moles of H_2O per mole of SO_2Cl_2	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ SO_2Cl_2(l.) (kcal.)	Wt. (g.)	Moles of H_2O per mole of SO_2Cl_2	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ SO_2Cl_2(l.) (kcal.)
0·9175	4100	−63·1	−93·3	1·2310	3100	−63·5	−92·9
0·8426	4500	−62·6	−93·8				
					Mean values	−63·1	−93·3

Recovery of chloride in the hydrolysis products was 99·4%.

(c) *Hydrolysis of thionyl chloride.*

Wt. (g.)	Moles of H_2O per mole of $SOCl_2$	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ $SOCl_2$(l.) (kcal.)	Wt. (g.)	Moles of H_2O per mole of $SOCl_2$	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ $SOCl_2$(l.) (kcal.)
1·1388	2900	−32·7	−58·3	0·9702	3400	−32·4	−58·6
0·7051	4700	−32·4	−58·6	1·0295	3200	−32·3	−58·7
					Mean values	−32·5	−58·5

Recovery of chloride in the hydrolysis products was 99·7%.

Discussion.—The mean value of $\Delta Hf PCl_3(l.) = -74·4$ kcal. is significantly different from the value of −79·6 kcal. obtained by simple hydrolysis and use of Thomsen's data for $\Delta Hf H_3PO_3$. A few experiments (not given in detail here) in which the heat of oxidation of hydrolysed phosphorus trichloride in bromine water was measured gave results in good agreement with those from the combined oxidation–hydrolysis of this chloride. Measurement of the heat of solution of crystalline phosphorous acid in aqueous hydrochloric acid

showed it to be approximately +1·0 kcal./mole, which is insufficient to account for the difference. Our view is that Thomsen's value is probably in error owing to the difficulty of obtaining very pure phosphorous acid.

The present results for sulphuryl chloride agree with that derived from Thomsen's work within the limits of our experiments, but there is a marked discrepancy between our results for thionyl chloride and those obtained by Ogier (*loc. cit.*), *viz.*, $\Delta H_{obs.}$ −39·2; $\Delta Hf°$ −49·2 kcal. Ogier's experimental details were not available, so we were unable to compare the dilutions in his experiments with those reported above. The $\Delta Hf°$ value calculated from Ogier's work is that given in the National Bureau of Standards, Circular 500.

The authors thank Messrs. A. F. Childs and J. M. Wright, who purified the materials used, and Miss M. Howells, who assisted in the calorimetry and analysis. Permission given by the Chief Scientist, Ministry of Supply, to publish these results is also acknowledged.

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The Ultra-violet Absorption of Triethyl Phosphite.

By M. HALMANN.

[Reprint Order No. 5146.]

DE HAUSS (*Chim. Analyt.*, 1952, **34**, 249) stated that solutions of trialkyl phosphites $(RO)_3P$ have pronounced ultra-violet absorption. For trimethyl phosphite in methanol and triethyl phosphite in hexane, maximum absorption is said to occur at 2600 Å and the minimum at about 2150 Å (see Fig. 1, *loc. cit.*). This result could be of value in the identification and determination of trialkyl phosphites in the presence of the isomeric dialkyl alkylphosphonates $R{\cdot}PO(OR)_2$ which do not absorb in this region.

On measuring the absorption of an ethanolic solution of triethyl phosphite prepared by the usual procedure from ethanol, phosphorus trichloride, and diethylaniline, an absorption curve was obtained which was similar in shape to that of De Hauss, but of much lower intensity: thus the molar extinction coefficient $\varepsilon = (1/cl) \log I_0/I$ (where c is the concentration of the phosphite in mole/l. and l the length of the cell in cm.) was only 1·45 for 2600 Å, while De Hauss reported the value of 14.

Since it is difficult to remove traces of diethylaniline from triethyl phosphite even after careful fractional distillation, it was considered possible that the above samples of triethyl phosphite were contaminated with the tertiary amine. Diethylaniline absorbs very strongly in the ultra-violet region: a 0·0001M-solution of diethylaniline in ethanol gave an absorption spectrum similar to that of a 1M-solution of our triethyl phosphite (cf. Bowden and Braude, *J.*, 1952, 1075).

It was possible to prepare pure triethyl phosphite which was almost transparent in the ultra-violet region by substituting triethylamine for diethylaniline in the synthesis of triethyl phosphite. The boiling point of triethylamine is much lower than that of triethyl phosphite and separation was easy by fractional distillation. The molar extinction coefficients of this triethyl phosphite in different solvents are tabulated below.

Solvent Å:	2700	2600	2500	2400	2300	2250
Methanol	0·013	0·030	0·065	0·234	0·446	1·32
Ethanol	0·067	0·083	0·14	0·29	0·47	1·31
n-Hexane	0·027	0·06	0·12	0·29	0·474	—
n-Heptane	0·013	0·016	0·045	0·194	0·271	1·09

It is thus not possible to use the ultra-violet absorption spectrum to distinguish between trialkyl phosphites and dialkyl alkylphosphonates.

For identification of diethyl ethylphosphonate in the presence of triethyl phosphite, the infra-red absorption spectrum is useful. The former substance absorbs strongly at

1230 cm.$^{-1}$, while triethyl phosphite is relatively transparent in the 1260—1180 cm.$^{-1}$ region (Meyrick and Thompson, *J.*, 1950, 225).

Experimental.—Triethyl phosphite was prepared as described by Ford-Moore and Perry (*Org. Synth.*, 1951, **31**, 111), except that freshly distilled triethylamine was substituted for diethylaniline. The product was fractionated four times through a semimicro-column (Gould, Holzmann, and Niermann, *Analyt. Chem.*, 1948, **20**, 361), b. p. 59°/19 mm. (Found: C, 43·7; H, 9·2. Calc. for $C_6H_{15}O_3P$: C, 43·4; H, 9·0%). The cuprous iodide addition compound had m. p. 112° (from ethanol) (Arbusow and Arbusow, *Ber.*, 1932, **65**, 195). The infra-red spectrum of this triethyl phosphite was identical with that described by Meyrick and Thompson (*loc. cit.*).

Solvents were purified as described previously (Dostrovsky and Halmann, *J.*, 1953, 505, 513). The ultra-violet absorption spectra were measured with a DU Beckmann Spectrophotometer.

The author is indebted to Dr. I. Dostrovsky for valuable criticism and advice, to Dr. S. Pinchas for the infra-red spectra, and to Mr. M. Wolcok for assistance with the preparation of materials.

WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, February 22nd,* 1954.]

OBITUARY NOTICE.

MILLICENT KING.

1900—1952.

MILLICENT KING was born on September 12th, 1900, in Dursley, Gloucestershire. She was a scholar at Redland High School, Bristol, and changed her course of study from arts to science to meet the need for scientists created by the First World War. She graduated with First Class Honours in Chemistry at Bristol University and obtained a Ph.D. degree in 1922 under Professor McBain. Her work with McBain consisted in investigations into the detergent action of soaps and a study of the surface conductivity of glass surfaces in solutions of potassium chloride. When McBain went to Stanford University in 1926, she became Secretary and Librarian to the Chemistry Department at Bristol with the title of Research Assistant.

Until 1939, she carried out a series of accurate measurements on the specific heats and heats of crystallisation of a number of homologous series, including hydrocarbons, fatty acids, methyl and ethyl esters, and amides. She also measured the heats liberated in the conversion of α- into β-forms in some series. The work was of importance in relation to the causes of the alternation in melting points of homologous series, and it was established that where there was alternation in the melting point there was also alternation in the heat of crystallisation. The effect was shown to lie in the different mode of orientation of the terminal group in the odd and the even series. The work was carried out at the same time as a parallel investigation by Dr. Piper, Dr. Malkin, and others on the *X*-ray spacings of homologous series, and contributed towards the elucidation of some doubtful points concerning their structure. Her results made it possible to calculate the convergence temperature for the melting points of long-chain compounds, and to derive a theory for their melting points.

Her experimental work ceased at the beginning of the Second World War, when her duties as Librarian and Secretary took up all her time. Her unselfish and untiring work as Secretary contributed greatly to the war effort and to the growth of the Chemistry Department since. In the Chemical Library she befriended many generations of students reading for their degrees.

She was a driver of an ambulance during the air raids of the last war.

She died on December 17th, 1952.

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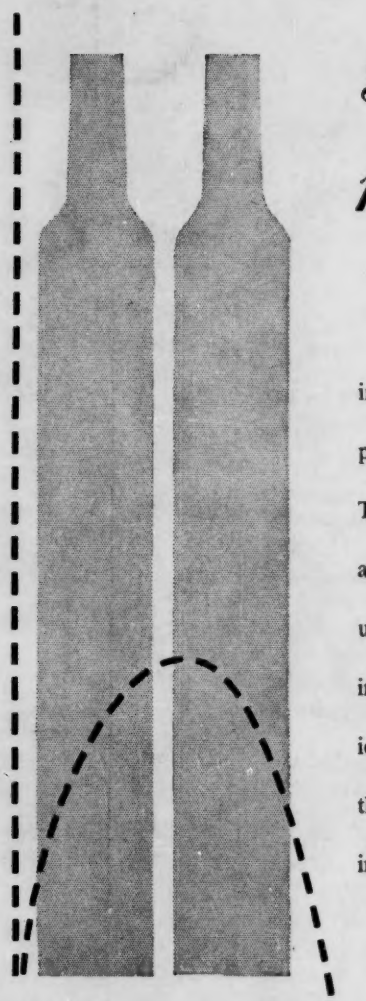

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